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CONFORM COPY

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

ALACER CORP., a California Corporation

Plaintiff,

vs.

FORTRESS SYSTEMS, LLC, a Nebraska Limited Liability Corporation DBA FSI NUTRITION

Defendant.

CASE NO. SACV09-01423 DOC (RNBx)

COMPLAINT FOR DECLARATORY RELIEF FOR PATENT INVALIDITY AND PATENT NON-INFRINGEMENT

Plaintiff ALACER CORPORATION hereby asserts the following claims against Defendant FORTRESS SYSTEMS, LLC DBA FSI NUTRITION.

INTRODUCTION

1. This complaint seeks a declaratory judgment of invalidity and non-infringement of U.S. Patent No. 6,294,579 ("the '579 Patent") under the provisions of 28 U.S.C. §§ 2201 and 2202 and the patent laws of the United

States, Title 35, United States Code. A copy of the '579 Patent is attached hereto as Exhibit A.

PARTIES

2. Plaintiff Alacer Corp. ("Plaintiff" or "Alacer") is a California corporation having its principal place of business at 80 Icon, Foothill Ranch, California 92610.

3. Upon information and belief, Defendant Fortress Systems, LLC DBA FSI NUTRITION ("Defendant" or "FSI") is a Nebraska limited liability corporation having its principal place of business at 2132 South 156th Circle, Omaha, Nebraska 68130.

JURISDICTION AND VENUE

4. This is a civil action for declaratory judgment that U.S. Patent No. 6,294,579 is invalid and/or not infringed. The Court has jurisdiction over the subject matter of this Complaint pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

5. The Court has personal jurisdiction over Defendant pursuant to the California Long Arm Statute, CA Civ. Proc. Code §410.10. Upon information and belief, Defendant transacts business in California and solicits business in this judicial district.

6. Venue in this judicial district is proper under 28 U.S.C. §§ 1391 and 1400.

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FACTUAL ALLEGATIONS

7. Plaintiff Alacer is a California corporation located in Orange County, California and provides nutritionally enhanced products that support an energetic, healthy lifestyle. It distributes energy products in powder and liquid shot form called "Emergen-C Alert! Energy & Focus Booster" ("Emergen-C Alert!"). Copies of the packaging of both the powder and liquid shot Emergen-C Alert products are attached hereto as Exhibit B.

8. Alacer requires a declaration of its rights and other legal relations with respect to a case of actual controversy concerning the '579 Patent that the '579 patent is invalid and/or not infringed.

9. The '579 Patent issued on September 25, 2001 and lists Joseph W. Carnazzo as the inventor. Records at the U.S. Patent Office show that FSI is the assignee. The '579 patent includes two independent claims (claims 1 and 12) and 17 dependent claims (dependent from claims 1 and 12). Independent claim 1 recites a method of promoting delivery of tyrosine supplementation into a human body, comprising the steps of dispensing a combination of an effervescent and a predetermined amount of tyrosine into a neutral pH liquid; dissolving the combination substantially in the liquid; and a human ingesting the liquid. Claim 12 recites a combination of an effervescent; and tyrosine mixed with the effervescent in an amount effective to enhance the solubility of the tyrosine in a pH neutral liquid and to enhance the rate of tyrosine absorption in a human when the human ingests the effervescent/tyrosine/liquid solution.

10. On November 10, 2009 counsel for FSI sent Alacer a letter claiming that the Emergen-C Alert! product is within one or more claims of the '579 Patent

and demanding that Alacer cease any and all sales of the Emergen-C Alert! products, destroy all Emergen-C Alert! products, and not manufacture, offer for sale, or sell any product that contains tyrosine and an effervescent in combination. FSI intimated that should Alacer refuse to cede to its demands, it will resort to litigation for infringement against Alacer. As such, Alacer has an immediate apprehension that FSI will commence litigation against Alacer.

11. Alacer has rejected Defendant's demands and has not directly infringed, contributorily infringed, or induced others to infringe any valid claim, if any, of the '579 Patent, either literally or under the doctrine of equivalents, willfully or otherwise, and further alleges that the '579 Patent is invalid by Defendant.

12. Alacer bases its allegations of invalidity on one or more printed publications pre-dating the '579 Patent, including Hitchcock, D., "The Solubility of Tyrosine in Acid and in Alkali," J. Gen. Phys. 747-757 (1924) ("Hitchcock") and U.S. Patent Nos. 5,560,928 ("the '928 Patent") and 6,071,539 ("the '539 Patent"), copies of which are attached as Exhibits C, D, and E, respectively.

13. Hitchcock discloses the solubility of tyrosine in acid and in alkali.

14. The '928 Patent discloses a composition for administration to a human containing an active ingredient such as an amino acid and an effective amount of an effervescent agent, and instructs dissolving the composition in water and administration to a human.

15. The '539 patent recites effervescent granules having an acidic agent, an alkaline agent, the ratio of which is determined according to the pH required

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for dissolving an active ingredient included in a formulation containing the effervescent granules, and combining the effervescent granules with an active ingredient such as an amino acid; reconstituting the effervescent and active ingredient formulation with water; and administering the formulation to a human.

16. As such, an actual justiciable controversy therefore exists between Defendant and Alacer concerning whether Alacer's Emergen-C Alert! product is within, or infringes, any valid claims of the '579 Patent, and whether one or more of the claims of the '579 Patent are invalid.

COUNT I

(Invalidity)

17. Alacer repeats and realleges the allegations contained in paragraphs numbered 1 through 16, as if fully set forth herein.

18. The '579 Patent and its claims have been, and are, invalid on the grounds that the subject matter sought to be patented therein fails to comply with the conditions and requirements for patentability set forth in Title 35, United States Code, including, but not limited to, the provisions of 35 U.S.C. §§ 102 and/or 103.

19. Failure to comply with the conditions and requirements for patentability under 35 U.S.C. §§ 102 and/or 103 is based upon one or more printed publications, including Hitchcock, the '928 Patent, and the '539 Patent.

20. Accordingly, there exists an actual justiciable controversy between Defendant and Alacer concerning whether the claims of the '579 Patent are invalid.

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21. Alacer requests a judgment declaring that the '579 Patent is invalid. Such a determination and declaration is necessary and appropriate at this time so that the parties may ascertain their respective rights and duties regarding the invalidity of the '579 Patent.

COUNT II

(Non-infringement)

22. In the alternative to Count I, Alacer repeats and realleges the allegations contained in paragraphs numbered 1 through 21, as if fully set forth herein.

23. Alacer has not, nor has it ever, directly infringed, contributorily infringed, or induced others to infringe any valid claim, if any, of the '579 Patent, either literally or under the doctrine of equivalents, willfully or otherwise.

24. Alacer's Emergen-C Alert! product is not covered by any valid claim, if any, of the '579 Patent, either literally or under the doctrine of equivalents.

25. Accordingly, there exists an actual justiciable controversy between Defendants and Alacer concerning whether any claims of the '579 Patent are infringed by Alacer's Emergen-C Alert! product in that Defendant claim that Alacer's Emergen-C Alert! product is within the scope of the claims of the '579 Patent, whereas Alacer denies that such is the case.

26. Alacer requests a judgment declaring that Alacer does not, and has not, directly infringed, contributorily infringed, or induced others to infringe the

'579 Patent. Such a determination and declaration is necessary and appropriate at this time so that the parties may ascertain their respective rights and duties regarding the non-infringement of the '579 Patent.

PRAYER FOR RELIEF

WHEREFORE, Alacer respectfully requests that this Court enter a judgment in its favor and against Defendants as follows:

(a) Declaring that each claim of U.S. Patent No. 6,294,579 is invalid by Defendant and without any force or effect against Alacer, its officers, agents, servants, employees, licensees, assigns, customers, and attorneys;

(b) In the alternative, declaring that Alacer does not infringe, and has not ever infringed any valid claim of U.S. Patent No. 6,294,579 directly, contributorily, or by inducement, willfully or otherwise;

(c) Deeming this to be an "exceptional case" within the meaning of 35 U.S.C. § 285, and awarding Alacer its attorney's fees, expenses and costs incurred herein;

(d) Awarding Alacer such other and further relief as this Court may deem just and proper.

Respectfully submitted,
CISLO & THOMAS LLP

Dated: December 4th, 2009

By: _____
Daniel M. Cislo, Esq.
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DEMAND FOR JURY TRIAL

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Alacer hereby requests a trial by jury on all the triable issues raised in this Complaint.

Respectfully submitted,
CISLO & THOMAS LLP

Dated: December 7th, 2009

By: _____
Daniel M. Cislo, Esq.
Kristin B. Kosinski, Esq.

Attorneys for ALACER CORP.

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US006294579B1

(12) **United States Patent**
Carnazzo

(10) **Patent No.: US 6,294,579 B1**
(45) **Date of Patent: Sep. 25, 2001**

(54) **METHOD FOR IMPROVING DELIVERY OF TYROSINE SUPPLEMENTATION**

(76) Inventor: **Joseph W. Carnazzo**, P.O. Box 150, Boys Town, NE (US) 68010

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/415,808**

(22) Filed: **Oct. 11, 1999**

(51) **Int. Cl.**[7] **A61K 31/195**
(52) **U.S. Cl.** **514/567**
(58) **Field of Search** 514/567

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Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Rothwell, Figg, Ernst & Manbeck

(57) **ABSTRACT**

The base compound for practicing the present invention is L-tyrosine effervescent powder, granules or tablet. Soluble effervescent powders, granules and tablets are prepared by blending and/or compression and contain, in addition to active ingredients mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent powders, granules and tablets should be stored in tightly closed containers or moisture-proof packs, labeled to indicate that they are not to be swallowed directly.

19 Claims, No Drawings

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METHOD FOR IMPROVING DELIVERY OF TYROSINE SUPPLEMENTATION

BACKGROUND OF THE INVENTION

1. Technical Field

This invention relates to a method of effervescent formulation for the promotion of tyrosine or a tyrosine precursor solubility, absorption and accuracy of measure for oral supplementation and its use with vitamin, mineral and nutritional supplements.

2. Description of the Related Art

Tyrosine is the amino acid precursor for the synthesis of the neurotransmitters norepinephrine and dopamine. A number of studies have shown that stress-induced depletion of brain norepinephrine is associated with performance deficit. Tyrosine appears to have a positive impact on stress-induced performance degradation in humans.

Tyrosine is a large, neutral amino acid found in dietary proteins. It is also formed in the liver and, to a limited extent, in the brain from phenylalanine, an essential amino acid. The hydroxylation of phenylalanine by phenylalanine hydroxylase forms tyrosine which is the precursor for the biosynthesis of the catecholamine neurotransmitters dopamine and norepinephrine. The recommended daily intake of phenylalanine is 2.2 grams. Tyrosine is found in both animal and vegetable protein with the level of tyrosine found in human food varying widely. Thus the total daily intake of tyrosine by an individual would vary according to the combination of animal and vegetable protein ingested.

The fundamental structural units of proteins are α-amino-acids, about 20 of which participate prominently in protein formation. These building-block molecules contain at least one carboxyl group and one α-amino group, but differ in the structure of the remainder of the molecule. All except the simplest one, glycine, are capable of existing in both D and L configurations with respect to their α-carbon but proteins contain only the L-enantiomers. The actual protein molecule consists of long-chain polymers which may be looked upon as having resulted from condensation of the amino acids thus producing amide (commonly called peptide) linkages. The number of amino acid molecules so condensed varies widely among different proteins, ranging from perhaps as few as 30 up to tens of thousands. Proteins are thus macromolecules which differ primarily from each other in the number of amino acid residues present and in the sequence of these in the polymer chain.

A neurotransmitter (NT) is defined as a chemical that is selectively released from a nerve terminal by an action potential, interacts with a specific receptor on an adjacent structure, and elicits a specific physiologic response. Most NTs derive from amino acids (or related compounds such as choline). Certain neurons synthesize only one, neuron-specific NT, others have been shown to synthesize 2 neurons or more NTs. Some neurons modify amino acids to form the "amine" transmitters (e.g., norepinephrine, serotonin); others combine amino acids to form "peptide" transmitters (e.g., endorphins, enkephalins); and still other neurons use amino acids unchanged or synthesized as transmitters. A few NTs are not related to amino acids.

Dopamine (DA) is the NT of some peripheral nerve fibers and of many central neurons (e.g., substantia nigra, midbrain, hypothalamus). The amino acid tryosine is taken up by dopaminergic neurons, converted by the enzyme tyrosine hydroxylase to 3,4-dihydroxyphenylalanine (dopa), decarboxylated by the enzyme aromatic L-amino acid decarboxylase to DA, and stored in vesicles. After release, DA interacts with dopaminergic receptors and is then pumped back by active processes (re-uptake) into the prejunctional neurons. DA levels are held constant by changes in tyrosine hydroxylase activity and the enzyme monoamine oxidase (MAO), which is localized in nerve terminals and metabolizes dopamine. DA is metabolized to several metabolites, including specifically homovanillic acid.

Norepinephrine (NE) is the NT of most postganglionic sympathetic fibers and many central neurons (e.g., locus ceruleus, hypothalamus). NE synthesis, like that of DA, also starts with the precursor tyrosine but continues as DA is hydroxylated by dopamine-beta-hydroxylase to form NE, which is stored in vesicles. Upon release, NE interacts with adrenergic receptors. This action is terminated largely by the re-uptake of NE back into the prejunctional neurons. Tyrosine hydroxylase and MAO regulate intraneuronal NE levels. Metabolism of NE occurs via MAO and catechol-O-methyltransferase to inactive metabolites (e.g., normetanephrine, 3-methoxy-4-hydroxyphenylethylene glycol, 3-methoxy-4-hydroxymandelic acid).

One of the factors which limits the extent of resistance the individual can mount apparently is his capacity to produce and respond to the neurotransmitter norepinephrine (NE). Studies with both animals and humans reveal that stress causes a sharp increase in the brain's use of NE because NE tracts are those activated by stress. This surge in use of NE tends to deplete available supplies, and as neural stores decline, so does the capacity to continue normal levels of performance. That the loss of NE is the cause and not merely the correlate of stress-induced behavioral decrements is suggested by the finding that biochemical reduction of NE even in the absence of stress can cause a reduction in performance similar to that caused by stress alone.

Tyrosine must compete with all the other large neutral amino acids for transport across the blood brain barrier. Therefore, the ratio of tyrosine to its amino acid competitors determines its rate of entry into the brain. Once in the brain, more is converted into NE if the neural circuits which require NE are activated. In other words, when the organism is at rest, excess tyrosine is not converted into a larger reserve pool of NE. But when the individual is under stress, available tyrosine is converted into NE at a faster rate to replenish expended NE. If sufficient tyrosine is not available to replace that which is used, NE and performance continue to decline.

This dietary-biochemical-neural pathway suggests a novel approach to slowing stress-induced performance degradation. If stress uses NE and NE decline reduces the level of functioning and performance, NE levels and performance can be restored by additional amounts of NE's precursor tyrosine.

A tyrosine dietary supplement is a realistic alternative to increasing NE levels for slowing stress-induced performance degradation. L-tyrosine is the most commonly used tyrosine supplement for oral consumption, although other tyrosine salts, tyrosine isomers, and synthetic tyrosine formulations exist. L-tyrosine supplementation of 100 mg/kg to 150 mg/kg were the most commonly used dosages in human studies. These dosages created maximal increases that were seen for 2 hours after tyrosine ingestion, thereafter catecholamine levels returned to base line. Supplemental tyrosine (100 mg/kg) has, in fact, been shown to enhance mental performance, improve mood, and diminish symptoms in human subjects exposed to such stressors as cold and high altitude. To achieve desired effects dosages of 7 to 15

grams of L-tyrosine will need to be consumed 1 hour prior to competition or intense exercise.

The problem with existing tyrosine supplements is that accurate dosage is difficult to achieve. This is so because tyrosine does not dissolve well in water or other neutral pH liquids and is very acid liable. This results in irregular dosage, inconsistent results, and limited absorption due to stomach acid destruction.

SUMMARY OF THE INVENTION

This method of promoting delivery of tyrosine, preferably a supplement of L-tyrosine or N-acetyl tyrosine, to the human body includes formation of tyrosine in an effervescent form which allows the tyrosine to dissolve and disperse into solution upon activation with water. The increase in solubility and dispersal gives a more uniform absorption of the product after ingestion. The effervescent form of tyrosine will buffer stomach acid, thus inhibiting stomach acid destruction of tyrosine after consumption. Because the tyrosine is in an effervescent powder packet, effervescent granule packet or tablet form, it offers a more accurate form of administration than bulk powders or suspensions. Tyrosine is soluble in alkaline solutions but does not readily dissolve in water or other neutral pH liquids. The effervescent form of tyrosine having an alkaline pH makes the tyrosine much more soluble in the liquid form. The use of flavorings in the effervescent method to deliver tyrosine is to be used to increase to palatability of the products.

It is therefore a general object of the present invention to provide a method of delivering a precise amount of tyrosine oral supplement to the human body.

It is another object of the invention to provide a tyrosine supplement that is more readily soluble and provides consistent results.

Still another object of the invention is to provide a tyrosine oral supplement that can be combined with other vitamins, minerals, and supplements for enhancement of health, nutrition, and related goals.

These and other objects will be obvious to those skilled in the art.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The inventor has discovered that tyrosine may be uniformly and accurately dispensed when completely dissolved and dispersed in liquid. More specifically, the tyrosine has been created in the form of an effervescent in tablet or particulate form which increases the pH of water to thereby increase the solubility of the tyrosine in the liquid.

L-tyrosine and N-acetyl tyrosine, as used in the prior art, do not readily dissolve in water or other neutral pH liquids. The combination of tyrosine and other chemicals to create an effervescent which, when combined with a proper measure of water, creates a liquid having an alkaline pH, making the tyrosine much more soluble in the liquid. The increase in solubility allows for more uniform absorption of the tyrosine after ingestion.

In addition, because the tyrosine is packaged in either tablet or premeasured particulate form, a precise amount of the compound is ingested. The prior art bulk powder form required the consumer to measure the proper amount of the product and dissolve the product in water. The precision of such measurement is uncertain. Furthermore, because prior art formulations of tyrosine required dissolution of tyrosine in a neutral pH liquid, non-uniform amounts of the tyrosine supplements are commonly undissolved and subsequently not ingested by the consumer. The result is non-uniform dosages and ingestion at non-uniform rates.

The use of a pre-measured effervescent assures complete dissolution and dispersal of the tyrosine and uniform rates of ingestion of the same. These goals are achieved by virtue of increasing the pH of the liquid and the agitation provided by the effervescence of the compound. The soluble effervescent will contain a mixture of acids, bicarbonates, and other agents which release carbon dioxide when dissolved in water.

The chemical formula for tyrosine is $C_9H_{11}NO_3$, and has a molecular weight of 181.19. Tyrosine is a dietary amino acid. In addition to its value as an energy substrate and in protein synthesis, it is a precursor to numerous biogenic amines and neurotransmitters.

Previously, tyrosine's use has been limited by its relative insolubility in water and susceptibility to stomach acid destruction. The use of effervescent technology, therefore, is employed to alter the pH of the water, giving tyrosine greater solubility in water and buffering stomach acid to limit tyrosine destruction.

The method of the present invention relies upon the combination of tyrosine with an effervescent to create an alkaline solution which is ingested by the consumer. The effervescent raises the pH to form an alkaline solution, whereby the tyrosine will uniformly dissolve and completely disperse in solution. In its preferred form, the invention includes a soluble effervescent containing tyrosine, at least one acid, and at least one bicarbonate for releasing carbon dioxide when dissolved in a neutral pH liquid, such as water. In the most preferred form of the invention, L-tyrosine or N-acetyl tyrosine is the type of tyrosine that is utilized.

The effervescent ingredients preferably utilize a mixture of acids, including citric acid and tartaric acid. Sodium bicarbonate or potassium bicarbonate may be utilized for the release of carbon dioxide. In addition, starch, flavoring agents, and lubricants for tablet compression are also utilized in the effervescent tablet. While the effervescent is preferably in the form of a tablet, it may also be utilized in a particulate form. The effervescent must be stored in a sealed container or other moisture-proof package, since water or other liquids will activate the effervescent. This also allows for a method of premeasuring the tyrosine dosage.

The effervescents are not to be swallowed directly, since they release carbon dioxide as they dissolve. Thus, the initial step in the method of the invention is to open the moisture-proof package containing the effervescent and dispense it into a container of water or other pH neutral liquid. Once the effervescent tyrosine has been dissolved and dispersed, the solution should be ingested immediately.

Thus, it can be seen that the invention accomplishes at least all of its stated objectives.

I claim:

1. A method of promoting delivery of tyrosine supplementation into a human body, comprising the steps of:

dispensing a combination of an effervescent and a predetermined amount of tyrosine into a neutral pH liquid;

dissolving the combination substantially in the liquid; and

a human ingesting the liquid.

2. The method of claim **1** wherein the dispensing step includes the initial step of opening a moisture-proof package containing the combination.

3. The method of claim **2** wherein the combination is in the form of a tablet.

4. The method of claim **2** wherein the combination is in the form of a premeasured particulate.

5. The method of claim **3** wherein the dispensing step includes dispensing the tablet in water.

6. The method of claim **4** wherein the dispensing step includes dispensing the particulate in water.

7. The method of claim **1** wherein the dispensing step includes dispensing the combination in water and the dissolving step includes the formation of an alkaline solution.

8. The method of claim **1** wherein the ingestive step is performed approximately one hour prior to assumption of vigorous activity by the human.

9. The method of claim **1** wherein the tyrosine is replaced by a tyrosine precursor.

10. The method of claim **9** wherein the tyrosine precursor is phenylalanine.

11. The method of claim **1** wherein the tyrosine is synthetic tyrosine.

12. In combination:

an effervescent; and

tyrosine mixed with the effervescent in an amount effective to enhance the solubility of the tyrosine in a pH neutral liquid and to enhance the rate of tyrosine absorption in a human when the human ingests the effervescent/tyrosine/liquid solution.

13. The combination of claim **12** wherein the effervescent is in the form of a tablet.

14. The combination of claim **12** wherein the effervescent is in the form of a particulate.

15. The combination of claim **12** wherein the effervescent includes an acid and a bicarbonate.

16. The combination of claim **15** wherein the acid is selected from the group consisting of citric acid and tartaric acid.

17. The combination of claim **15** wherein the bicarbonate is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

18. The combination of claim **12** comprising an effervescent tablet including:

Tyrosine 0.5 grams–6 grams

Citric Acid 1 grams–12 grams

Sodium Bicarbonate 0.6 grams–7.2 grams; and

Potassium Bicarbonate 0.4 grams–3.6 grams.

19. The combination of claim **18** comprising an effervescent tablet including:

Tyrosine 500 mg;

Citric Acid 100 mg;

Sodium Bicarbonate 600 mg;

Potassium Bicarbonate 400 mg;

Sorbitol/Mannitol 850 mg;

Fruit Flavor 150 mg;

Aspartame 35 mg;

Mineral Oil 35 mg; and

Sodium Lauryl Sulfate 8 mg.

* * * * *

Directions: As a dietary supplement, and to maximize energy, drink 1 bottle daily all at once. Shake well before opening.

Supplement Facts

Serving Size 2.5 fl oz (74 mL)

Amount Per Serving		% DV
Calories	25	
Total Carbohydrate	6 g	2%**
Sugars	6 g	
Vitamin C (as ascorbic acid)	250 mg	417%
Niacin	2.5 mg	13%
Vitamin B_6 (as pyridoxine hydrochloride)	5 mg	250%
Folic Acid	500 mcg	125%
Vitamin B_{12} (as methylcobalamin, cyanocobalamin)	112.5 mcg	1,875%
Pantothenic Acid (as calcium pantothenate)	12.5 mg	125%
Calcium (as calcium gluconate, calcium lactate, calcium pantothenate)	25 mg	3%
Magnesium (as magnesium lactate gluconate)	30 mg	8%
Zinc (as zinc amino acid chelate)	1 mg	7%
Manganese (as manganese gluconate)	0.25 mg	13%
Chromium (as chromium polynicotinate)	5 mcg	4%
Sodium (as Okinawa deep sea minerals)	30 mg	1%
Potassium (as potassium citrate)	100 mg	3%
Proprietary Energy and Focus Complex	1115 mg	†

Green Tea Extract, Lecithin, Schisandra Extract, Dimethylaminoethanol Bitartrate, D-Ribose, Stevia (leaf extract), Malic Acid, L-Theanine (Suntheanine®), Taurine, Glycerophosphatidylcholine, Citicoline, L-Carnitine Tartrate, L-Tyrosine, Adenosine 5'-Triphosphate Disodium, CoQ10, Cayenne Pepper Powder, Alpha Lipoic Acid, Quercetin, Vinpocetine

** Percent Daily Values (DV) are based on 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Purified water, cane sugar, natural flavors, blueberry juice powder, citric acid, raspberry juice powder, tapioca maltodextrin, silica, glycine, aspartic acid, and tartaric acid. **CONTAINS MILK AND SOY.**

CAUTION: Contains green tea which contains caffeine, comparable to a cup of coffee or tea. Caffeine products may cause nervousness, sleeplessness, and occasional rapid heartbeat.

Do not use if you are pregnant or nursing or under 12 years of age.

Emergen-C Alert, Energy Liquid Shot, Drink Mix, Focus Boost

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Emergen-C

SEND TO A FRIEND EMERGENC.COM SEARCH

EMERGEN-C® SHOT EMERGEN-C IMMUNE+™ EMERGEN-C ALERT!® STORES JOIN

Directions: As a dietary supplement, and to maximize energy, mix one packet daily with 4-5 oz. of water.

Supplement Facts

Serving Size 1 Packet (9.4 g)

Amount Per Serving		% DV
Calories	25	
Total Carbohydrate	6 g	2%**
Sugars	6 g	
Vitamin C (as ascorbic acid, zinc ascorbate, chromium ascorbate)	250 mg	417%
Thiamin (as thiamine hydrochloride)	0.19 mg	13%
Riboflavin (as riboflavin 5'-phosphate sodium)	0.22 mg	13%
Niacin	2.5 mg	13%
Vitamin B_6 (as pyridoxine hydrochloride)	5 mg	250%
Folic Acid	500 mcg	125%
Vitamin B_{12} (as methylcobalamin, cyanocobalamin)	112.5 mcg	1,875%
Pantothenic Acid (as calcium pantothenate)	12.5 mg	125%
Calcium (as calcium carbonate, calcium phosphate, calcium pantothenate)	25 mg	3%
Phosphorus (as potassium phosphate, calcium phosphate, sodium phosphate)	19 mg	2%
Magnesium (as magnesium hydroxide, magnesium carbonate)	25 mg	6%
Zinc (as zinc ascorbate)	1 mg	7%
Manganese (as manganese gluconate)	0.25 mg	13%
Chromium (as chromium ascorbate)	5 mcg	4%
Sodium (as sodium bicarbonate, sodium phosphate)	30 mg	1%
Potassium (as potassium bicarbonate, potassium carbonate, potassium phosphate)	85 mg	2%
Proprietary Energy and Focus Complex	1445 mg	†
Malic Acid, Green Tea Extract, Lecithin, Schisandra Extract, Dimethylaminoethanol Bitartrate, D-Ribose, Stevia (leaf extract), L-Theanine (Suntheanine®), Taurine, Glycerophosphatidylcholine, Citicoline, L-Carnitine Tartrate, L-Tyrosine, Adenosine 5'-Triphosphate Disodium, CoQ10, Cayenne Pepper Powder, Vinpocetine, Alpha Lipoic Acid, Quercetin		

** Percent Daily Values (DV) are based on 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Cane sugar, fructose, natural flavors, citric acid, fruit and vegetable juice colors, blueberry juice powder, tapioca maltodextrin, silica, raspberry juice powder, glycine, aspartic acid, tartaric acid, and cysteine hydrochloride. **CONTAINS MILK AND SOY. CAUTION:** Contains green tea which contains caffeine, comparable to a cup of coffee or tea. Caffeine products may cause nervousness, sleeplessness, and occasional rapid heartbeat. Do not use if you are pregnant or nursing or under 12 years of age.

Emergen-C Alert, Energy Liquid Shot, Drink Mix, Focus Boost

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THE SOLUBILITY OF TYROSINE IN ACID AND IN ALKALI.

By DAVID I. HITCHCOCK.

(*From the Laboratories of The Rockefeller Institute for Medical Research.*)

(Received for publication, May 6, 1924.)

I.

INTRODUCTION.

Many amphoteric electrolytes form soluble salts with acid or alkali, while the undissociated or isoelectric substances themselves are often only slightly soluble in water. It should, therefore, be possible to calculate the solubility of such a substance from its ionization constants as an acid and as a base and from the hydrogen ion concentration of the saturated solution. The theory underlying this dependence of the solubility on the hydrogen ion concentration has been outlined by Michaelis,[1] who stated, however, that the only experimental investigations of the question have consisted in determinations of the pH at which the solubility was a minimum. A few measurements were made by Beveridge[2] of the solubility of anthranilic acid in hydrochloric acid, but the work was hardly extended far enough to determine whether the increased solubility could be theoretically explained. Cohn and Hendry[3] studied the effect of hydrogen ion concentration on the solubility of casein in very dilute solutions of sodium hydroxide, but this case was complicated by the fact that the constitution, molecular weight, and basicity of the ampholyte were unknown. Accordingly it seemed advisable to measure the solubility in acid and in alkali of a comparatively simple ampholyte of known constitution, with the object of testing the theoretical relation between the solubility and hydrogen

[1] Michaelis, L., Die Wasserstoffionenkonzentration, Berlin, 2nd edition, 1922, 73, 58.

[2] Beveridge, H. H., *Proc. Roy. Soc. Edinburgh*, 1908–09, xxix, 648.

[3] Cohn, E. J., and Hendry, J. L., *J. Gen. Physiol.*, 1922–23, v, 521.

ion concentration. The substance used in this work was *l*-tyrosine, or para-hydroxyphenyl-α-amino-propionic acid, $HO \cdot C_6H_4 \cdot CH_2 \cdot CHNH_2 \cdot COOH$.

II.

EXPERIMENTAL PROCEDURE.

The tryosine was prepared from commercial casein hydrolyzed by boiling with hydrochloric acid, following the procedure of Abderhalden[4] (who, however, used silk as the raw material). The product was decolorized with animal charcoal, recrystallized three times from hot water, and dried with alcohol and ether. Its nitrogen content, determined by the Kjeldahl method, was found to be 7.73 per cent; calculated, 7.733.

Saturated solutions of tyrosine in HCl or NaOH of various concentrations were obtained by placing 100 cc. of the solvent in contact with an excess of solid tyrosine in 150 cc. Pyrex flasks closed tightly by rubber stoppers, and rotating the flasks, end over end, for 1 or 2 days in a water bath at 25°C. $\pm$ 0.05°. Preliminary measurements of the solubility gave identical values after 1 and after 2 days in the thermostat. In the case of pure water it was found that equilibrium was reached more slowly; concordant values were obtained only after 3 days agitation of tyrosine with supersaturated and undersaturated solutions. The solutions were filtered with suction through hardened filter paper fastened by a rubber band over the end of a glass tube about 6 mm. in diameter, which was connected by rubber tubing to a pipette. This made it possible to conduct the filtration without removing the flasks from the thermostat.

The concentration of tyrosine in the saturated solutions was obtained by Kjeldahl determinations of nitrogen, using 100 cc. Kjeldahl flasks with 2 cc. of concentrated H_2SO_4, 0.5 cc. of 5 per cent $CuSO_4$, 1 gm. of K_2SO_4, and a few pieces of broken alundum to prevent bumping. For the lower concentrations of tyrosine 25 cc. samples were used; for the higher concentrations, suitable aliquot parts. After the addition of 50 cc. of water and 6 cc. of 1:1 sodium

[4] Abderhalden, E., *Z. physiol. Chem.*, 1912, lxxvii, 75.

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hydroxide solution, the ammonia was distilled into 25 cc. of N/50 HCl, and determined by titration with N/50 NaOH, using methyl red as indicator. The blanks obtained with the reagents varied from 0.2 to 0.3 cc. N/50. Duplicate analyses generally agreed to within 0.1 cc. N/50. Each solubility determination represents the mean of two analyses; the figure for tyrosine and water is the mean of those obtained from eight separate solutions.

The hydrogen ion concentrations were determined by electromotive force measurements with Clark electrodes in an air thermostat at 25°C. They are based on the value 1.035 for the pH of 0.1000 M HCl, and on the assumption that contact potential differences were eliminated by the use of saturated KCl. The concentrations of hydroxyl ions in the alkaline solutions were calculated from the pH measurements, using the value $k_w = 1 \times 10^{-14}$ for the ion product of water at 25°.

The concentrations of HCl and NaOH given are those of the original solutions with which the tyrosine was shaken. It was found by direct titration, using methyl red, that the solution of the tyrosine did not appreciably change these values.

The results are given in Tables I and II.

III.

DISCUSSION OF RESULTS.

The results obtained with hydrochloric acid are plotted in Fig. 1. It is evident that the solubility of tyrosine is a linear function of the initial concentration of hydrochloric acid, and also of the final concentration of hydrogen ion. That this is predicted by the theory may be shown as follows. Representing tyrosine by TOH, in acid solutions it will ionize as a base:

$$TOH \rightleftarrows T^+ + OH^-$$

Applying the law of mass action,

$$\frac{[T^+]\,[OH^-]}{[TOH]} = k_b$$

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Since $[H^+]\,[OH^-] = k_w$, the ion product of water, letting $K = \frac{k_b}{k_w}$ $s_0 = [TOH]$, $h = [H^+]$, and $t = [T^+]$, it follows that

$$K = \frac{t}{s_0 h} \tag{1}$$

TABLE I.

Solubility of Tyrosine in Hydrochloric Acid.

Concentration of HCl, mols per liter × 10^3.	Concentration of tyrosine, mols per liter × 10^3.	pH	Concentration of hydrogen ion, mols per liter × 10^3.
0	2.62	5.1 to 5.5	0.01
1.00	3.09	3.19	0.65
2.00	3.25	2.857	1.39
4.99	4.10	2.457	3.49
9.99	5.39	2.160	6.92
20.00	8.43	1.861	13.8
30.00	10.8	1.675	21.1
40.00	13.8	1.560	27.6
50.00	16.5	1.450	35.5

TABLE II.

Solubility of Tyrosine in Sodium Hydroxide.

Concentration of NaOH, mols per liter × 10^3.	Concentration of tyrosine, mols per liter × 10^3.	pH	Concentration of hydroxyl ion, mols per liter × 10^5.
0	2.62	5.1 to 5.5	0.000
0.98	3.54	8.342	0.220
1.95	4.30	8.865	0.731
4.88	7.06	9.249	1.775
9.76	10.7	9.484	3.05
19.5	17.5	9.726	5.32
29.9	24.7	9.841	6.94
39.8	30.4	9.881	7.60
49.8	35.8	9.953	8.98

The total solubility of tyrosine, s, is equal to the concentration of the undissociated molecule plus that of the tyrosine chloride formed, or

$$s = s_0 + \frac{t}{d_s} \tag{2}$$

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if d_s = the degree of dissociation of the salt formed. The total concentration of hydrochloric acid, a, is equal to that of the free hydrochloric acid remaining plus that of the tyrosine chloride formed, or

$$a = \frac{h}{d_a} + \frac{t}{d_s} \tag{3}$$

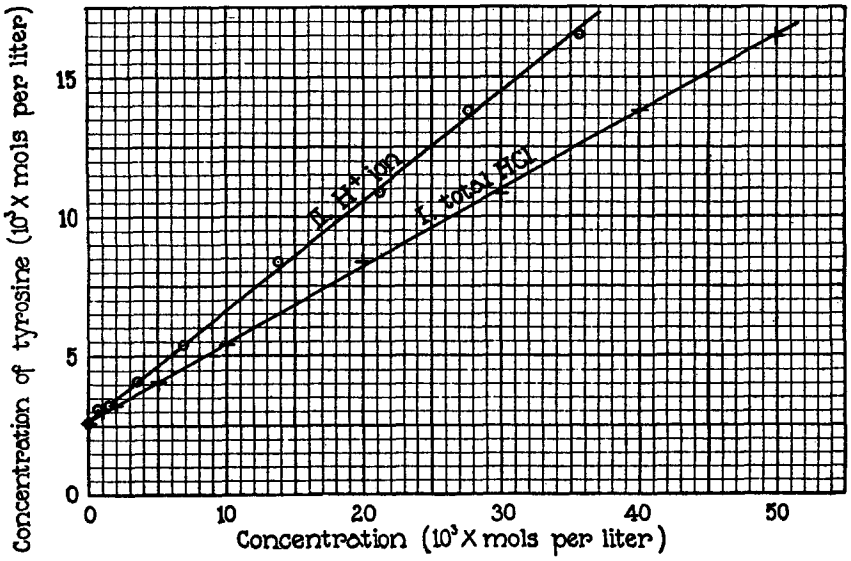

FIG. 1. Effect of the concentration of total HCl and of H^+ ion on the solubility of tyrosine. The curves are linear, as the theory requires for a mono-acid base.

where d_a is the degree of dissociation of the hydrochloric acid. By combining these three equations the following expression is obtained for s in terms of a.

$$s = s_0 + \frac{K s_0}{\frac{d_s}{d_a} + K s_0} a$$

Assuming that $d_s = d_a$ (which should be approximately true in accordance with the isoionic principle and the rule of equal ionization for strong electrolytes of the same type[5]), the relation becomes

[5] Washburn, E. W., Principles of physical chemistry, New York and London, 1st edition, 1915, 317, 295, 220.

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$$s = s_0 + \frac{K s_0}{1 + K s_0} a \tag{4}$$

This equation indicates the linear relationship between s and a, in Curve I of Fig 1. Evidently s_0 is, within the experimental error, equal to the solubility of tyrosine in pure water, and the slope of the line is $\frac{K s_0}{1+Ks_0}$.

By combining equations (1) and (2) a relation between s and h can be obtained, which is

$$s = s_0 + \frac{K s_0}{d_s} h$$

This is a linear equation only if d_s is constant. If the approximate assumption is made that $d_s = 1$, then

$$s = s_0 + K s_0 h \tag{5}$$

Equation (5) thus represents the line which is Curve II of Fig. 1, s_0 being the solubility of tyrosine in water, and Ks_0 being the slope of the line.

It is also possible to show that a linear relation exists between h and a. By combining equations (1) and (3) it follows that

$$a = h\left(\frac{1}{d_a} + \frac{K s_0}{d_s}\right)$$

If it is assumed that $d_a = d_s = 1$, then

$$a = h\,(1 + K s_0) \tag{6}$$

Equations (4), (5), and (6) can be tested by using the experimental values of s_0, s, a, and h to calculate K, and hence k_b, which is the product of K and k_w. The results of this calculation are given in Table III, using 1.0×10^{-14} as the value of k_w at 25°. The best value for k_b, 1.57×10^{-12}, is probably more reliable than the value 2.6×10^{-12}, which was found by Kanitz.[6] The older value was obtained by the conductivity method, which involves a doubtful estimation of the conductivity of unhydrolyzed tyrosine chloride. Attempts to obtain this quantity by experiment in this laboratory have been fruitless.

[6] Kanitz, A., *Arch. ges. Physiol.*, 1907, cxviii, 539.

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TABLE III.

Basic Ionization Constant of Tyrosine.

Valves for $k_b \times 10^{12}$ as calculated from.			s (observed) $\times 10^3$.	s (calculated) $\times 10^3$.
a and s.	h and s.	h and a.		
			2.62	2.62
(3.4)	(2.8)	(2.1)	3.09	2.89
1.8	1.7	1.7	3.25	3.19
1.6	1.6	1.6	4.10	4.06
1.5	1.5	1.7	5.39	5.47
1.6	1.6	1.7	8.43	8.29
1.4	1.5	1.6	10.8	11.3
1.5	1.6	1.7	13.8	14.0
1.5	1.5	1.6	16.5	17.2
Mean....1.56	1.57	1.66	$k_b = 1.57 \times 10^{-12}$	

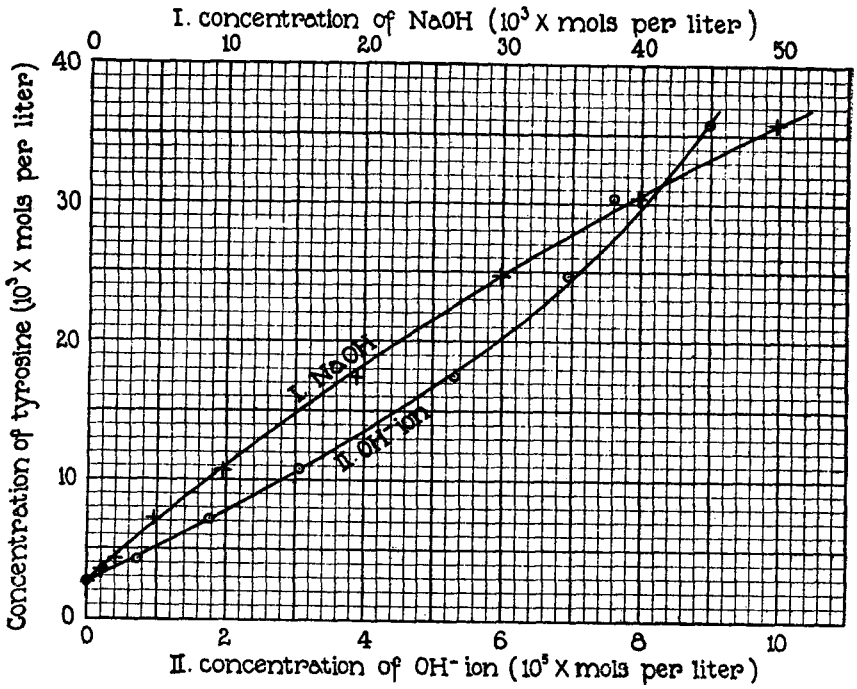

FIG. 2. Effect of the concentration of total NaOH and of OH^- ion on the solubility of tyrosine. The curves are not linear because tyrosine is a dibasic acid.

The constancy of the values for k_b indicates the extent to which the experimental data agree with the theory and the assumptions made. The agreement of the observed values of s with those calculated from equation (5) indicates more directly, perhaps, that the data are satisfactorily explained by the theory.

The results obtained with tyrosine and sodium hydroxide are plotted in Fig. 2. Here the curves are not linear; and the explanation for this is to be found in the fact that tyrosine acts as a dibasic acid, the phenol group as well as the carboxyl group losing hydrogen ions.

Representing the total concentration of sodium hydroxide by b, its degree of ionization by d_b, the ionization of monosodium tyrosinate by d_1, the concentration of its negative ion by t_1, the ionization of disodium tyrosinate by d_2, and the concentration of its negative ion by t_2, the following equations result from the application of the law of mass action to the ionization of tyrosine as a dibasic acid.

$$\frac{t_1\, h}{s_0} = k_{a1} \tag{7}$$

$$\frac{t_2\, h}{t_1} = k_{a2} \tag{8}$$

$$\frac{t_2\, h^2}{s_0} = k_{a1}\, k_{a2} \tag{9}$$

It follows also that

$$b = \frac{k_w}{h d_b} + \frac{t_1}{d_1} = \frac{2\, t_2}{d_2} \tag{10}$$

$$s = s_0 + \frac{t_1}{d_1} + \frac{t_2}{d_2} \tag{11}$$

Substituting the values of t_1 and t_2 from equations (7) and (9), and making the somewhat doubtful assumption that $d_b = d_1 = d_2 = 1$, we have

$$b = \frac{k_w}{h} + \frac{k_{a1}\, s_0}{h} + \frac{2\, k_{a1}\, k_{a2}\, s_0}{h^2} \tag{12}$$

and

$$s = s_0 + \frac{k_{a1}\, s_0}{h} + \frac{k_{a1}\, k_{a2}\, s_0}{h^2} \tag{13}$$

By combining equations (12) and (13) it is possible to calculate approximate values for k_1 and k_2. Thus it would follow that

$$b - s = \frac{k_w}{h} + \frac{k_{a1} k_{a2} s_0}{h^2} - s_0$$

and

$$b - 2s = \frac{k_w}{h} - 2s_0 - \frac{k_{a1} s_0}{h}$$

from which

$$k_{a1} = \left(\frac{k_w}{h} + 2s - 2s_0 - b\right)\frac{h}{s_0} \tag{14}$$

and

$$k_{a1} k_{a2} = \left(b + s_0 - s - \frac{k_w}{h}\right)\frac{h^2}{s_0} \tag{15}$$

It is to be noted that equations (7) to (11) are exact, while equations (12) to (15) are only approximate, since they contain the assumption of complete ionization. However, the values of k_{a1} and k_{a2} calculated from equations (14) and (15) exhibit a certain degree of constancy, as is shown in Table IV. The table contains also a comparison of the observed values of s with those calculated from equation (13), using the mean values for k_{a1} and k_{a2} and the observed values for s_0 and h.

The complete expression for the solubility of tyrosine at any hydrogen ion concentration is

$$s = s_0\left(1 + \frac{k_b h}{k_w} + \frac{k_{a1}}{h} + \frac{k_{a1} k_{a2}}{h^2}\right) \tag{16}$$

If the values already given for the constants are substituted, this becomes

$$s = 0.00262\left(1 + 157\,h + \frac{7.8 \times 10^{-10}}{h} + \frac{6.6 \times 10^{-20}}{h^2}\right) \tag{17}$$

The curve in Fig. 3 represents values of s calculated from this equation, plotted as a function of the pH. The circles represent the values of s experimentally determined.

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TABLE IV.

Acidic Ionization Constants of Tyrosine.

$k_{a1} \times 10^{10}$	$k_{a1}k_{a2} \times 10^{20}$	s (observed) $\times 10^3$.	s (calculated) $\times 10^3$.
(14.9)	(47)	3.54	3.08
7.4	(18)	4.30	4.20
8.7	5.1	7.06	6.79
8.1	6.8	10.7	10.5
7.4	6.1	17.5	18.4
7.9	6.1	24.7	25.2
8.0	7.9	30.4	28.2
7.1	7.8	35.8	34.9
Mean....7.8	Mean....6.6	$k_{a1} = 7.8 \times 10^{-10}$ $k_{a2} = 8.5 \times 10^{-11}$	

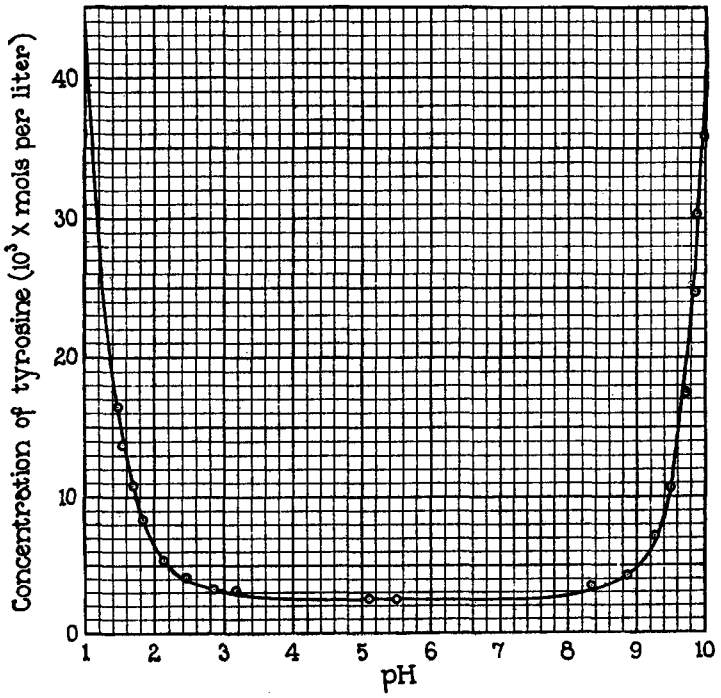

FIG. 3. Effect of pH on solubility of tyrosine. The points represent observed values; the curve represents values calculated from the theory.

In equation (16) the expression in parentheses is the reciprocal of the quantity designated by Michaelis[7] as ρ, the unionized fraction of the ampholyte, which in the notation used here is $\frac{s_0}{s}$ By differentiating his expression with respect to h and placing the derivative equal to zero, an equation can be derived for the hydrogen ion concentration at the isoelectric point, as was done by Michaelis for the case of an ampholyte with only one acidic group. Substituting the values of the constants, this calculation gives for the isoelectric point

$$h^3 = 5 \times 10^{-12} h + 8.4 \times 10^{-22} \quad (18)$$

From the shape of the curve in Fig. 3, the isoelectric point would appear to lie between pH 5 and 6. If this is the case the last term in equation (18) is negligible, and the value for h becomes 2.23×10^{-6}, corresponding to pH 5.65. The same value is obtained by the equation of Michaelis, which considers from the start only one acid and one basic ionization constant. In such a case as this, however, as Michaelis has pointed out, the exact location of the isoelectric point has little significance, since the ampholyte is isoelectric or almost completely undissociated over a broad zone of pH values.

SUMMARY.

Measurements have been made of the solubility at 25°C. of tyrosine in hydrochloric acid and in sodium hydroxide solutions varying from 0.001 to 0.05 M, and also in distilled water. The pH of the saturated solutions was measured with the hydrogen electrode. The following values for the ionization constants of tyrosine have been obtained from the measurements: $k_b = 1.57 \times 10^{-12}$, $k_{a1} = 7.8 \times 10^{-10}$, $k_{a2} = 8.5 \times 10^{-11}$. The changes in solubility with pH can be satisfactorily explained by the use of these ionization constants.

[7] Michaelis[1], p. 54.

US005560928A

United States Patent [19]

DeFelice

[11] Patent Number: 5,560,928

[45] Date of Patent: Oct. 1, 1996

[54] **NUTRITIONAL AND/OR DIETARY COMPOSITION AND METHOD OF USING THE SAME**

[76] Inventor: **Stephen L. DeFelice**, 235 Munsee Way, Westfield, N.J. 07090

[21] Appl. No.: **494,100**

[22] Filed: **Jun. 23, 1995**

[51] **Int. Cl.**[6] **A61K 9/16**; A61K 9/22

[52] **U.S. Cl.** **424/466**; 424/468; 424/469; 424/470; 424/489; 424/490; 424/495; 514/781

[58] **Field of Search** 424/466, 468, 424/469, 470, 458, 461, 489, 490, 495

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Primary Examiner—James M. Spear
Attorney, Agent, or Firm—Watov & Kipnes, P.C.

[57] **ABSTRACT**

A composition and method of using the same which provides in as little as a single dose covering a 24 hour period a nutritional and/or dietary supplement which provides administration of water soluble and water insoluble active ingredients for immediate and sustained-release delivery.

28 Claims, No Drawings

NUTRITIONAL AND/OR DIETARY COMPOSITION AND METHOD OF USING THE SAME

FIELD OF THE INVENTION

The present invention is directed to a nutritional/dietary composition capable of providing at least one nutritional and/or dietary supplement including free form and sustained-release compounds in solid or liquid dosage form.

BACKGROUND OF THE INVENTION

It has become increasingly important for the prevention and treatment of disease as well as the maintenance of good health for people to supplement the normal intake of food with nutritional and/or dietary supplements. Typically, these substances are required to be taken several times a day in order to fulfill the daily dosage requirements. Many nutritional and/or dietary substances are not well stored by the body requiring frequent dosing. However, the more doses required, the less compliance there is by the patient. People simply will not take the number of pills required to complete the daily dosage requirements. The reasons for failing to take proper dosages include inconvenience, difficulty in swallowing pills, forgetfulness and the like. In addition, the generally poor taste of many nutritional and/or dietary substances adds to the difficulty in completing dosage regimens.

There have been efforts to develop dosage systems which seek to make active ingredients more pleasant and effective for the consumer. In order to provide a pleasant tasting composition and one which provides the desired benefits, it is necessary for the nutritional and/or dietary dosage system meet the following requirements.

The system must provide for both nutritional and dietary active ingredients. The system must also be able to deliver both water soluble and water insoluble active ingredients. A sustained-release system must also be provided so that active ingredients which are required to be administered over a long period may be slowly delivered rather than all at once. The formulation must be readily dissolvable in a liquid, particularly water to provide a pleasant tasting drink. Finally, administration of the composition must be sufficient to provide an optimum delivery of the active ingredients so that the composition is effective until the next dosage which may be as much as approximately 24 hours later.

Efforts have been made to meet the above-stated criteria of a nutritional and/or dietary supplement formulation. For example, Nakomoto, U.S. Pat. No. 3,773,920, discloses sustained-release granules which provide for a water soluble medicament contained within an ethylcellulose polymer to provide uniform release velocity and complete release of the medicament.

Huber, U.S. Pat. No. 4,122,157, discloses a preparation for the administration of nitrofurantoin. The composition is in the form of a sustained-release tablet which is taken orally. The tablet contains a rapid release component and a slow release component for the same drug. It is further stated that the composition contains an effervescent agent.

Glassman, U.S. Pat. No. 4,503,031, discloses a two section tablet for the administration of drugs including a sustained-release component. Sodium bicarbonate is employed as an effervescent agent.

Ashmead, U.S. Pat. No. 4,725,427, discloses a vitamin-mineral combination for both water soluble and water insoluble active ingredients. An effervescent agent is provided so that the composition is dissolvable in water.

Briggs et al., U.S. Pat. No. 4,752,479, disclose an iron containing dietary supplement for oral administration in which an inner core contains iron and a waxy film former of ethylcellulose is provided around the core.

Barry et al., U.S. Pat. No. 5,055,306, disclose an effervescent tablet which includes a sustained-release formulation comprising a core containing the active ingredient and a coating which is water swellable.

Wehling et al., U.S. Pat. No. 5,178,878, disclose an effervescent composition for oral administration which employs microparticles of an active ingredient including vitamins and minerals.

Radebaugh et al., U.S. Pat. No. 5,200,193, disclose tablets which contain a sustained-release formulation using ethylcellulose as a matrix. The tablets contain drugs such as ibuprofen as the active ingredient.

Hagemann et al., U.S. Pat. No. 5,211,957, disclose an effervescent tablet for diclofenac providing both immediate and delayed release of the active ingredient.

Wehling et al., U.S. Pat. No. 5,223,264, disclose an oral pediatric vitamin supplement in tablet form containing an effervescent agent.

Zema et al., U.S. Pat. No. 5,306,506, disclose a water composition containing a drug as an active ingredient which is microencapsulated to delay release and mask the taste of the active ingredient. Ethylcellulose is used as a membrane for the microencapsulation.

Eichel et al., U.S. Pat. No. 5,376,384, disclose a sustained-release formulation for water soluble drugs employing a diffusion barrier.

While all of these references disclose dosage formulations effectively administering an active ingredient through tablet or liquid form, none of the references provide an acceptable means of administering a nutritional and/or dietary supplement in as little as a single daily dosage form which can accommodate both water soluble and water insoluble nutritional and/or dietary active ingredients and provide a system by which the same can be delivered both immediately and through sustained-release.

SUMMARY OF THE INVENTION

The present invention is generally directed to a pharmaceutical composition for providing a dosage formulation for the administration of nutritional and/or dietary supplements as few as once in a 24 hour period.

In particular, the present invention is directed to a nutritional/dietary composition comprising:

(a) at least one active ingredient selected from the group consisting of a nutritional supplement, a dietary supplement and combinations thereof in an amount sufficient to provide a dosage form of said active ingredients as few as once in a 24 hour period, said active ingredients being in the form of both a free form component and a microencapsulated component which is in a sustained release form; and

(b) an effective amount of an effervescent agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a composition uniquely suited for patients requiring a nutritional and/or dietary supplement. The present invention provides a for-

mulation which delivers a sufficient amount of the active ingredients including water soluble compounds, water insoluble compounds and combinations and variations thereof to provide a dosage form so that the patient need take the supplement as little as only once during a 24 hour period. The patient therefore need not be concerned with taking several pills during the day with the possibility of missing a dose and thereby reducing the effectiveness of the therapy. The present invention is particularly suited to those who have difficulty in swallowing the pills and/or the elderly because the present formulation can be provided in liquid form.

The active ingredients which may be employed in the present invention include nutritional supplements, dietary supplements and combinations thereof. The compounds meeting this criteria may have varying degrees of solubility in water ranging from highly soluble to insoluble. These compounds generally include vitamins, minerals, amino acids, herbal and botanical products and the like. Vitamins generally refer to organic substances that are required in the diet and include thiamin, riboflavin, nicotinic acid, pantothenic acid, pyrodoxine, biotin, folic acid, vitamin B_{12}, lipoic acid, ascorbic acid (vitamin C), vitamin A, vitamin D, vitamin E and vitamin K as well as coenzymes thereof.

Minerals include inorganic substances which are required in the human diet and include calcium, iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium, and the like and mixtures thereof.

Dietary supplements include, for example, B pollen, bran, wheat germ, kelp, cod liver oil, ginseng, fish oils, amino acids, protein and the like and mixtures thereof.

The preferred nutritional and/or dietary supplements for employment in the present invention include carnitine, calcium, magnesium, ascorbic acid and vitamin E. Carnitine is a naturally occurring amino acid required for mitochondrial oxidation of long-chain fatty acids and is found in all human tissue including skeletal muscle, the liver and the heart. Its role is to transport fatty acids across mitochondrial membranes to be metabolized resulting in the production of ATP (energy). Ingestion of carnitine raises blood levels thereof but does not enhance the clinical-biochemical effects of the naturally occurring carnitine already in the heart when the heart is functioning normally.

During myocardial ischemia, however, carnitine is lost from the ischemic portion of the myocardium. The naturally occurring blood levels of carnitine are not high enough to replenish the carnitine lost in the ischemic portion of the myocardium during an ischemic attack. It has been demonstrated that exogenously administered carnitine, which leads to increased blood levels results in the replenishment of carnitine in the ischemic portion of the myocardium.

Carnitine is a highly water soluble water substance that after absorption is quickly excreted by the kidneys. Therefore there is only a relatively short period in which blood levels of carnitine are sufficient to reenter the ischemic myocardium leading to only temporary protection.

Magnesium, like carnitine, is water soluble and rapidly excreted. A very high percentage of diabetics have magnesium deficiency. This results in a chronic state of increased platelet aggregation and increased sensitivity to angiotensin II. Increased platelet aggregation leads to increased blood clotting and increased angiotension II sensitivity leads to increased vasoconstriction. Both of these effects lead to a decreased blood supply thereby reducing the delivery of natural substances to their intended receptor sites. Multiple daily doses have been required to reverse replenished magnesium stores and normalize the aforementioned abnormalities.

One of the main functions of vitamin E is to enter the lipid layer of arteries to reduce free radical activity thereby reducing the rate of atherosclerosis. Magnesium deficiency will decrease the availability of vitamin E to such receptor sites because of increased blood clotting and vasoconstriction.

In each situation, the present invention provides a substantially continuous supply of nutritional and/or dietary supplements (e.g. carnitine, magnesium, vitamin E and the like) to ensure sufficient blood levels over extended periods of time.

The amount of the active ingredient can be selected in accordance with the current state of the art regarding nutritional and/or dietary substances. The amount of the active ingredient should be chosen to provide the patient with a sufficient amount to meet the requirements of the consumer if the composition is delivered as little as once over a 24 hour period. By way of example, carnitine is provided in an amount from about 0.075 to 20 grams, preferably 0.5 to 6 grams. Calcium is provided in an amount of from about 0.01 to 3.0 grams, preferably 0.5 to 2.0 grams. Magnesium may be present in the composition of the invention in an amount of from about 0.1 to 3.0 grams, preferably 0.2 to 1.0 gram. Ascorbic acid is generally present in an amount of from about 0.01 to 3.0 grams, preferably 0.075 to 1.0 gram. Vitamin E may be present in an amount of from about 10 to 3000 IU, preferably 30 to 1000 IU.

The active ingredients in accordance with the present invention are in the free form of the compound and in a substantially sustained-release form (i.e. microencapsulated). By way of example, the free form compounds may be water soluble while the sustained-release compounds may be water insoluble.

Microencapsulation of the active ingredient is a process in which the active ingredient is coated with a continuous film of a natural or synthetic polymer. Methods of microencapsulation are known such as described in A. Lieberman Pharmaceutical DOSAGE FORMS: TABLETS—Volume I, Second Edition, New York (1989) pp. 372–376. One such method is by the addition of a non-solvent of the polymer and then hardening of the membrane so that the microcapsule can be separated from the vehicle by filtration or centrifuging or the like. The rate of delivery of the encapsulated active ingredient can be controlled as a function of the type of polymer used to encapsulate the active ingredients, the thickness of the polymer layer or both.

Another method of microencapsulating an active ingredient includes processing three mutually immiscible phases, one containing the active ingredient, one containing the microencapsulating coating material (e.g. ethyl cellulose) and one containing a liquid vehicle used only in the manufacturing phase. The three phases are mixed and the coating material is thereby absorbed on the active ingredient. The next step involves converting the coating material to a substantially solid form by cross-linking or the like.

Microencapsulation of a water insoluble substance can also function to mask unpleasant tastes but is principally used in the present invention for slowing down the rate of release of the active ingredient to provide a sustained-release formulation.

The microencapsulated active ingredient will generally comprise from about 3% to 50% by weight of the encapsulating polymer and from about 50% to 97% of the active ingredient. The polymer constituting the encapsulating

membrane must be permeable or soluble in the gastrointestinal juices in order to allow the release of the active ingredient and its absorption.

The polymers which may be employed in the present invention for microencapsulating the active ingredient include polyacrylates, polymethacrylates, polyvinylchloride, polyvinylalcohol, polyethylene, polyamides, polysiloxanes, cellulose derivatives including ethylcellulose and the like. Ethylcellulose is the preferred polymer for microencapsulation.

The effervescent agent employed in the present composition serves to evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent agent to the saliva in the mouth or to water or other suitable liquid. The gas generating reaction is typically the result of the reaction of a soluble acid source and an alkali metal or alkaline earth metal carbonate or carbonate source. The reaction of these two compounds produces carbon dioxide gas upon contact with water.

The acid sources generally include food acids, acid anhydrides and acid salts. Food acids include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids, combinations thereof and the like. Acid anhydrides of the above acids may also be used. The acid salts typically are selected from sodium, dihydrogen phosphate, disodium dihydrogen pyrophosphate, acid citrate salts and sodium acid sulfite.

The carbonate sources include dry solid carbonate and bicarbonate salts such as sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, magnesium carbonate, sodium sesequicarbonate, sodium glycine carbonate, L-lysine carbonate, arginine carbonate and amorphous calcium carbonate.

The amount of the acid component and the bicarbonate component can vary over a wide range. Generally, equal amounts of the two components of the effervescent agent are preferred.

The amount of the effervescent agent in the composition of the present invention can also vary over a wide range. For the formation of tablets, the effervescent agent will typically comprise from about 5 to 50% by weight of the final composition. The amount of the effervescent agent should be sufficient to produce a rapid and complete disintegration of the formulation when placed in water. Disintegration should occur in water without stirring or other mechanical means for dissolution.

The present composition may include one or more additives chosen typically from flavors, colors, binders, fillers, disintegrants and the like. Examples of binders include acacia, tragacanth, gelatin, starch and the like.

Disintegrants include starches, bentonite, gums, alginates and the like.

Coloring agents are those suitable for food and include both natural and synthetic coloring agents.

Flavors which may be incorporated into the present composition are selected from natural and synthetic oils and flavor aromatics or combination thereof including extracts from plants, leaves, flowers, fruits and the like. Typical flavoring agents include cinnamon oil, oil of wintergreen, peppermint oils, clove oil and the like.

The amount of the individual additives may vary over and under range. Binders can be present in amounts up to 60% by weight of the composition. Coloring agents are typically present in an amount of no more than up to 3.5% by weight of the total composition.

In typical cases, the total amount of the additives does not exceed about 25% by weight of the composition.

The nutritional and/or dietary composition of the present invention can generally be prepared by first preparing the effervescent agent (e.g. sodium bicarbonate and citric acid) in dry form.

A microencapsulated form of the active ingredient (e.g. magnesium chloride, vitamin E, carnitine) is combined with the free form amount of each ingredient. A mixture of the effervescent agent and the active ingredients in both microencapsulated and free form are combined and formed into suitable tablets.

Tablets incorporating the composition of the present invention can be prepared by well known tabletting methods. For example, the composition is deposited into a cavity and then a compressive force is applied by a punching device. The tabletted material is thus formed into the shape formed by the punching device and the cavity.

EXAMPLE 1

A quantity of sodium bicarbonate sufficient to provide one gram per tablet is passed through a one mm screen and then loaded into a fluid bed. Deionized and sterile water (filtered through a ligacon membrane) into the fluid bed immediately with the commencement of the injection of dry air through the inlet of the fluid bed. The dry air inlet is accompanied with the nebulization of at least 5.5 liters of water at a pressure of around 8 atm for about 10 to 12 minutes. Then the sodium bicarbonate is dried with dry air at a temperature of 33° to 40° C. to form a granulate.

When the internal temperature of the granulate reaches room temperature the influx air is stopped and citric acid (1.3 g per tablet) is added directly into the fluid bed. The mixture is homogenized and sterile water is nebulized into the vessel while under mixing. The granulate is dried in dry air (50° C.) until a final temperature of the granule (45° to 50° C.) is reached. The warming up of the dry air is stopped, but the incoming stream of air is continued until the granule is at a temperature of 30° C.

Vitamin C, Vitamin E and magnesium oxide are micro encapsulated in the following manner:

0.4 g of ascorbic acid, 400 I.U of vitamin E and 0.5 g of magnesium oxide are granulated in a vessel. A solution of cellulose acetophthalate is added to the vessel under stirring to form a granulate of the respective active ingredients.

The granulate is dispersed in demineralized water under stirring so that cellulose acetophthalate precipitates on the agglomerated particles with the salification of the solution. Subsequently an acid solution is injected to complete the coating operation and to initiate hardening of the microencapsulation coating. The product is filtered, dried in a fluid bed and passed through a screen to select microcapsules of the desired size. The microcapsules are combined with suitable amounts of the free form of each of the active ingredients (i.e. amounts similar to those used for forming microcapsules). The dry mixture of both the free and microencapsulated forms of the active ingredients is pressed into tablets in a humidity controlled area at a temperature of about 20° C. The resulting tablets contain the active ingredients in both free form and microencapsulated form in the presence of the effervescent agent.

EXAMPLE 2

The process of Example 1 is repeated except that the active ingredients used to form the microcapsules are added

to an organic medium such as cyclohexane. A solution of ethyl cellulose is added to the vessel under stirring to form a granulate of the respective active ingredients. The granulate is then cooled to harden the coating of the microcapsules. The product is then filtered, dried in a fluid bed and passed through a screen to select microcapsules of the desired size.

EXAMPLE 3

The process of Example 1 is repeated except that the active ingredients include carnitine tartrate and ascorbic acid wherein the amounts of each of the active ingredients for both the free and microencapsulated form components are 3.0 g and 0.5 g per tablet.

What is claimed is:

1. A composition comprising:

(a) at least one active ingredient including carnitine in amounts sufficient to provide a dosage form of said active ingredient as few as once in a 24 hour period, said active ingredients being in both a free form component and a microencapsulated component which has sustained-release properties; and

(b) an effective amount of an effervescent agent.

2. A composition comprising:

(a) at least one active ingredient including anyone of calcium, magnesium, ascorbic acid, vitamin E and combinations thereof in amounts sufficient to provide a dosage form of said active ingredient as few as once in a 24 hour period, said active ingredients being in both a free form component and a microencapsulated component which has sustained-release properties; and

(b) an effective amount of an effervescent agent.

3. A method of providing to a warm-blooded animal a nutritional or dietary supplement or combination thereof, comprising administering to said warm-blooded animal the composition of claim **2**.

4. The composition of claim **1** wherein the active agent is selected from the group consisting of carnitine, calcium, magnesium, ascorbic acid, vitamin E and combinations thereof.

5. The composition of claim **1** in the form of a tablet or granules dissolvable in water.

6. The composition of claim **1** wherein the microencapsulated component comprises said active ingredient contained within a polymer coating.

7. The composition of claim **6** wherein the polymer coating is made of ethylcellulose.

8. The composition of claim **1** wherein carnitine is present in an amount of from about 0.75 to 20 grams.

9. The composition of claim **4** wherein calcium is present in an amount of 0.01 to 3.0 grams.

10. The composition of claim **4** wherein magnesium is present in an amount of from about 0.1 to 3.0 grams.

11. The composition of claim **4** wherein ascorbic acid is present in an amount of from about 0.01 to 3.0 grams.

12. The composition of claim **1** wherein vitamin E is present in an amount of from about 10 to 3000 IU.

13. The composition of claim **1** wherein the effervescent agent is the combination of an acid and an alkali metal or alkaline earth metal carbonate.

14. The composition of claim **1** wherein the active ingredients are selected from water soluble compounds, water insoluble compounds and combinations thereof.

15. The composition of claim **14** wherein the free form component is water soluble.

16. The composition of claim **14** wherein the sustained-release component is water insoluble.

17. A method of providing to a warm-blooded animal a nutritional or dietary supplement or combination thereof, comprising administering to said warm-blooded animal the composition of claim **1**.

18. The composition of claim **2** wherein the sustained-release component is water insoluble.

19. The composition of claim **2** wherein the active agent further includes carnitine.

20. The composition of claim **2** in the form of a tablet or granules dissolvable in water.

21. The composition of claim **2** wherein the microencapsulated component comprises said active ingredient contained within a polymer coating.

22. The composition of claim **21** wherein the polymer coating is made of ethylcellulose.

23. The composition of claim **2** wherein calcium is present in an amount of 0.01 to 3.0 grams.

24. The composition of claim **2** wherein magnesium is present in an amount of from about 0.1 to 3.0 grams.

25. The composition of claim **2** wherein ascorbic acid is present in an amount of from about 0.01 to 3.0 grams.

26. The composition of claim **2** wherein vitamin E is present in an amount of from about 10 to 3000 IU.

27. The composition of claim **2** wherein the effervescent agent is the combination of an acid and an alkali metal or alkaline earth metal carbonate.

28. The composition of claim **2** wherein the free form component is water soluble.

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United States Patent [19]

Robinson et al.

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[45] **Date of Patent: Jun. 6, 2000**

[54] **EFFERVESCENT GRANULES AND METHODS FOR THEIR PREPARATION**

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[52] **U.S. Cl.** **424/466**; 424/464; 424/489; 424/490

[58] **Field of Search** 424/405, 464, 424/465, 466, 489, 490, 497

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[57] **ABSTRACT**

According to the present invent, effervescent granules having a controllable rate of effervescence are provided. Such granules comprise an acidic agent, an alkaline agent, a hot-melt extrudable binder capable of forming a eutectic mixture with the acidic agent and, optionally, a plasticizer. The effervescent granules are made by a hot-melt extrusion process.

16 Claims, No Drawings

EFFERVESCENT GRANULES AND METHODS FOR THEIR PREPARATION

The present application claims priority to provisional application Ser. No. 60/026,991, filed Sep. 20, 1996.

FIELD OF THE INVENTION

This invention relates to an effervescent composition and a method of preparing same. More specifically, it relates to an effervescent granule having a controllable rate of effervescence, the granule being made by a hot-melt extrusion process.

BACKGROUND OF THE INVENTION AND DESCRIPTION OF THE PRIOR ART

Effervescent granules have found a variety of uses over the years. These include dental compositions containing enzymes, contact lens cleaners, washing powder compositions, beverage sweetening tablets, chewable dentifrices, denture cleaners, surgical instrument sterilizers, effervescent candies, as well as many pharmaceutical formulations such as for analgesics, antibiotics, ergotamines, digoxin, methadone and L-dopa.

Film-coated effervescent granules are known in the art. Polymers such as cellulose acetate phthalate or hydroxypropyl methylcellulose have been used. Such coatings have been introduced in order to increase tablet stability as well as to control dissolution rate and to target particular regions of the gastrointestinal tract.

Hot-melt extrusion as a method of preparing pharmaceutical formulations has previously been disclosed; however, effervescent formulations prepared by hot-melt extrusion are not known.

Hot-melt extrusion processes in the art have generally required extremely elevated temperatures (>150° C.), which temperatures could degrade extruded materials. It has not been appreciated that effervescent compositions, which are inherently heat labile, can be hot-melt extruded without significant degradation or decompaction.

Lindberg (Acta. Pharm. Suec. (1988), 25, 239–246) teaches a continuous wet granulation method for preparing effervescent granules. The process includes the steps: (1) mixing powdered citric acid and $NaHCO_3$ in the hopper of a Baker Perkins cooker extruder and granulating the mixture with ethanol.

U.S. Pat. No. 4,153,678 and British Patent Application Laid-Open No. 2083997 disclose effervescent tablets for addition to animal drinking water, respectively containing levamisole and vitamins or minerals as active components. U.S. Pat. No. 3,667,929 discloses that, an effervescent powdery composition coated by pulverizing active components such as piperazine acid salt, copper sulfate or sodium nitrate, an acid substance and carbonate together with a hydrophobic or a slowly dissolving material, is useful as an agent for addition to animal drinking water or a material for horticultural use.

Effervescence can be defined as the evolution of bubbles of gas in a liquid. As set forth in chapter 6 of Pharmaceutical Dosage Forms: Tablets Volume I, Second Edition. A. Lieberman. ed. 1989, Marcel Dekker, Inc. (the entirety of which is hereby incorporated by reference), effervescent mixtures have been known and used medicinally for many years. As discussed in this text, and as commonly employed, an effervescent tablet is dissolved in water to provide a carbonated or sparkling liquid drink. In such a drink the effervescence helps to mask the taste of medicaments. However, the use of effervescent tablets to prepare a beverage including medicaments, is not convenient. It requires preparatory steps before administration of the drug and also requires the presence of a suitable mixing container.

Effervescent tablets have also been used in the dental area. Westlake, U.S. Pat. No. 1,262,888, Howell, U.S. Pat. No. 3,962,417 and Aberg U.S. Pat. No. 4,753,792 disclose effervescent dentifrice tablets adapted to foam in the mouth of a patient so as to provide a tooth cleansing action.

An effervescent dosage form which incorporates microparticles which are susceptible to rupture upon chewing or which are adapted to provide substantially immediate release of the pharmaceutical ingredients contained in the microparticles is disclosed in U.S. Pat. No. 5,178,878 to Wehling et al. The microparticles comprise a drug encapsulated in a protective material. The microparticles are then mixed with an effervescent agent and then the mixture compressed into tablets.

Kond et al., in U.S. Pat. No. 5,223,246, disclose a water soluble effervescent composition prepared by hot-melting (1) an active component and (2) an acid and a carbonate for effervescent, with (3) a water soluble adjuvant whose melting point is not lower than 40° C., for addition to drinking water. The effervescent composition was prepared by mixing the active agent, the acid, the carbonate and the water soluble adjuvant and then heating the entire mixture to melt the adjuvant and subsequently cooling the mixture to room temperature while stirring to form effervescent particles.

Thus, there is no teaching or suggestion in the art of preparing effervescent granules by hot-melt extrusion. Despite prior efforts towards developments of suitable effervescent granules, there have been unmet needs heretofore for improved effervescent granules having controllable rates of effervescence and for methods for their preparation.

SUMMARY OF THE INVENTION

The present invention provides an effervescent granule having a controllable rate of effervescence prepared by hot-melt extruding (i) an acidic agent, (ii) an alkaline agent, and (iii) a hot-melt extrudable binder which melting or softening point temperature is less than about 150° C. and which is capable of forming a eutectic mixture with the acidic agent. The acidic and alkaline agents should be able to effervesce when placed in an aqueous solution. A formulation according to this aspect of the invention can provide a rate of release of an active ingredient that ranges from immediate to a delayed or controlled release over a prolonged period of many hours.

One aspect of the present invention provides a solid pharmaceutical dosage form adapted for direct oral administration, i.e., for direct insertion into the mouth of a patient. A dosage form according to this aspect of the present invention includes a mixture incorporating a water and/or saliva activated effervescent granule having a controllable rate of effervescence and a therapeutic compound.

According to another aspect of the present invention, it has been found that combination of the effervescent granules with the other ingredients can provide effective taste masking of particularly poor tasting compounds. This aspect of the invention thus provides a dosage form which offers both immediate or extended release and effective taste masking.

The effervescent granules taught herein can be used in pharmaceutical, veterinary, horticultural, household, food, culinary, pesticidal, agricultural, cosmetic, herbicidal, industrial, cleansing, confectionery and flavoring applications.

Formulations incorporating the effervescent granules according to one aspect of the present invention can further include one or more additional adjuvants and/or active ingredients which can be chosen from those known in the art including flavors, diluents, colors, binders, filler, surfactant, disintegrant, stabilizer, compaction vehicles, and non-effervescent disintegrants. The effervescent granules themselves do not generally include therapeutic compounds or other active ingredients.

The present invention also provides a method of preparing an effervescent granule having a controllable rate of effervescence where the method comprises mixing and hot melt extruding a hot-melt extrudable binder and an acidic agent to form a eutectic mixture which eutectic mixture is then mixed and hot-melt extruded with an alkaline agent to form the effervescent granule. The hot-melt extrusion process herein advantageously allows for extremely short exposure times of compounds to elevated temperatures as well as a higher throughput than batchwise hot-melt methods.

Other features, advantages and embodiments of the invention will be apparent to those skilled in the art from the following description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "effervescent granules" means granules that consist of an effervescent couple and a suitable hot-melt extrudable binder and that are prepared by hot-melt extrusion. By "effervescent couple" is meant a combination of an acidic agent and an alkaline agent that when combined in the presence of water cause the formation of a gas such as carbon dioxide, oxygen or chlorine dioxide.

The effervescent granules of this invention can be in the state of powder or fine particles to increase the dissolution rate, and preferably a particle size such that 90% or more passes a 16 mesh (1,000μ) screen, and more preferably a particle size such that more than 90% passes a 18 mesh (850 mu m) screen. Generally, the larger the effervescent granule, the longer it will take to completely disintegrate. This is particularly true when there are low levels of effervescent couple present in the granules.

Effervescent Granule Components

As used herein, "effervescence" means the evolution of bubbles of gas from a liquid as the result of a bubble or gas generating chemical reaction. The bubble or gas generating reaction of the effervescent couple in the effervescent granule is most often the result of the reaction of an acidic agent and an alkaline agent. The reaction of these two general classes of compounds produces a gas upon contact with water.

As used herein, the term "acidic agent" refers to any compound or material that can serve as a proton source and can react with the alkaline agent of the invention to form a gas causing a solution containing them to effervesce. The acidic agent can have more than one acid dissociation constant, i.e. more than one acid functional group. The acidic agent can be any organic or inorganic acid in the free acid, acid anhydride and acid salt form. An acidic agent which is in solid state at room temperatures and shows pH 4.5 or lower when saturated into water at room temperatures or its acid alkali metal salts (e.g. sodium salt, potassium salt, etc.) can be employed. As the acidic agent for the effervescent granule, a compound which is not harmful to animals including man is desirably employed. The acidic agent can be tartaric acid, citric acid, maleic acid, fumaric acid, malic acid, adipic acid, succinic acid, lactic acid, glycolic acid, alpha hydroxy acids, ascorbic acid, amino acids and their alkali hydrogen acid salts. And, even in the case of an acid substance such as phosphoric acid or pyrophosphoric acid or other inorganic acids which is liquid or in liquid state at room temperature, when their acid alkali metal salts are solid at room temperature, those acid alkali metal salts can be employed as acidic agents. Among the above-mentioned acidic agents, those having a relatively large acid dissociation constant (10^3 or more) and a small hygroscopicity (critical humidity at 30° C. is 40% RH or more) are preferably employed.

It is preferred if the acidic agent can form a eutectic mixture with a binder. Because these acids are directly ingested, their overall solubility in water is less important than it would be if the effervescent granules of the present invention were intended to be dissolved in a glass of water.

As used herein, the term "alkaline agent" means an alkaline compound that releases a gas, or causes a solution to effervesce, when exposed to a proton source such as an acidic agent or water. The alkaline agent can be a carbon dioxide gas precursor, an oxygen gas precursor or a chlorine dioxide gas precursor.

When the alkaline agent is a carbon dioxide precursor, compounds such as carbonate, sesquicarbonate and hydrogencarbonate salts (in this specification, carbonate and hydrogencarbonate, or bicarbonate, are generically referred to as carbonate) of potassium, lithium, sodium, calcium, ammonium, or L-lysine carbonate, arginine carbonate, sodium glycine carbonate, sodium amino acid carbonate can be used. When the alkaline agent is an oxygen gas precursor, compounds such as anhydrous sodium perborate, effervescent perborate, sodium perborate monohydrate, sodium percarbonate and sodium dichloroisocyannurate can be used. When the alkaline agent is a chlorine dioxide (ClO_2) precursor, compounds such as sodium hypochlorite and calcium hypochlorite can be used. ClO_2 can be used as a chemical sterilizer in cleansing operations.

Where the effervescent agent includes two mutually reactive components, such as an acidic agent and an alkaline agent, it is preferred, although not necessary, that both components react completely. Therefore, a ratio of components which provides for equal amounts of reaction equivalents is preferred. For example, if the acid used is diprotic, then either twice the amount of a mono-reactive carbonate alkaline agent, or an equal amount of a all-reactive alkaline agent should be used for complete neutralization to be realized. However, in other embodiments of the present invention, the amount of either the acidic agent or the alkaline agent can exceed the amount of the other component. This can be useful to enhance taste and/or performance of a tablet containing an overage of either component.

By controlling the relative ratio of acidic agent: alkaline agent, the effervescent granules can be used to regulate the pH of their environment. Thus, the present granules can be used to regulate the pH of body cavities such as the mouth, rectum or vagina.

The ratio of the above-mentioned acidic agent and alkaline agent can also be determined according to the pH required for dissolving an active ingredient included in a formulation containing effervescent granules or upon other conditions which a user can contemplate. When the solubility of the active ingredient increases at the acid side, the pH of the solution is lowered by adding the acidic agent in an amount more than equivalent to the alkaline agent. When the solubility of the active ingredient increases at the basic side, the pH of the solution is raised by adding the alkaline

agent in an amount more than equivalent to the acidic agent. In either case, the pH near the acidic agent immediately after the dissolution is low, while the pH near an alkaline agent is high. In a case where the solubility of an active ingredient does not depend on pH, the ratio of an acidic agent and an alkaline agent can be optionally selected.

The amount of carbon dioxide precursor, i.e. alkaline agent, to be incorporated is proportional to the volume of carbon dioxide gas generated. When it is desired to increase the dissolution rate of an active ingredient included in a formulation containing effervescent granules, it can be advantageous to increase the amount of carbon dioxide precursor accordingly, and the amount is usually selected from the range of from about 3% to about 70%, preferably from about 10% to 70% by weight based on the effervescent granule.

An acidic agent and a carbon dioxide precursor are used respectively in a powdery or granular state, usually 90% or more of them being capable of passing through a 100 mesh (150μ) screen. The particle size of the binder used will usually be about 100 mesh (150μ). In any case, it is generally acceptable that the additional amount of either component can remain unreacted.

As used herein, the term "hot-melt extrudable" refers to a compound or formulation that can be hot-melt extruded. A hot-melt extrudable binder is one that is sufficiently rigid at standard ambient temperature and pressure but is capable of deformation or forming a semi-liquid state under elevated heat or pressure. Although the formulation of the invention need not contain a plasticizer to render it hot-melt extrudable, plasticizers of the type described herein can be included.

Examples of hot-melt extrudable binders which can be used in the effervescent granules include acacia, tragacanth, gelatin, starch, cellulose materials such as methyl cellulose and sodium carboxy methyl cellulose, alginic acids and salts thereof, polyethylene glycol, guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC F68, PLURONIC F127), collagen, albumin, gelatin, cellulosics in nonaqueous solvents, and combinations of the above and the like. Other binders include, for example, polypropylene glycol, polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, polyethylene oxide and the like.

Binders may be used in an amount of up to about 60 weight percent and preferably about 3 to about 8 weight percent of the total composition. All binders used in this invention are hot-melt extrudable. While the melting and/or softening point temperatures of these binders usually rise with increase of their molecular weights, preferable ones are those with a melting or softening point temperature less than about 150° C. However, binders having melting or softening points greater than about 150° C. can be used. Hot-melt extrudable binders having a melting or softening point temperature greater than about 150° C. will require use of a plasticizer during hot-melt extrusion such that the binder melting or softening point temperature will be lowered below 150° C. Among the above-mentioned binders, polyethylene glycol is preferable, and that having a molecular weight of about 1000 to 8000 Da is more preferable.

The binder can be used in any form such as powder, granules, flakes or heat-molten liquid. While the amount of binder to be added can be modified, it is usually present in an amount less than about 10% by weight and preferably in the range of about 3–8% by weight of the granule.

By "controllable rate of effervescence" is meant that the rate of effervescence can be controlled such that either a rapid, intermediate or slow rate of effervescence by an effervescent granule is achieved. The rate of effervescence by an effervescent granule is controlled as detailed below.

When referring to the rate of effervescence as "rapid", it is understood that the effervescent granules of the present invention should disintegrate in an aqueous solution in less than 10 minutes, and desirably between about 15 seconds and about 7 minutes. In a particularly preferred embodiment according to the present invention, the effervescent granules should dissolve in an aqueous solution in between about 8 seconds and about 5 minutes. Disintegration time can be approximated by observing the disintegration time of the effervescent granules immersed in water at about 37° C. The disintegration time is the time from immersion to substantially complete the effervescent granules as determined by visual observation. As used in this disclosure the term "complete disintegration" of the effervescent granules refers to the dissolution or disintegration of the effervescent granules. Disintegration times referred to in this disclosure should be understood as determined by the method used herein unless otherwise specified.

When referring to the rate of effervescence as "intermediate," it is understood that the effervescent granules of the invention should disintegrate in an aqueous solution in more than about 10 minutes and less than about 1 hour.

When referring to the rate of effervescence as "slow," it is understood that the effervescent granules of the present invention should disintegrate in an aqueous solution in about 1 hour to about 4 hours.

Control of the rate of effervescence can be achieved by varying the relative amounts of the components in the effervescent granule. Thus, by increasing the amount of hot-melt extrudable binder relative to the total weight of the effervescent granule, a less friable and stronger granule can be generally prepared. Conversely, by decreasing the amount of hot-melt extrudable binder relative to the total weight of the effervescent granule, a more friable or weaker granule can be generally prepared. Hydrophobic binders will generally tend to have a greater impact upon granule hardness than hydrophilic binders.

Generally, forming a eutectic mixture between the acidic agent and the hot-melt extrudable binder before hot-melting extruding with the alkaline agent will yield effervescent granules that are harder and thus slower dissolving than those prepared by hot-melt extruding the binder, acidic agent and alkaline agent components together simultaneously.

Having an excess of either the acidic agent or alkaline agent in the effervescent granule will generally result in increased rate of effervescence when compared to an effervescent granule having the same amounts, on an equivalent basis, of both agents. Regardless of whether either agent is in excess, the total amount of gas produced by an effervescent granule will not exceed the theoretical amount of gas produced by the agent serving as the limiting reagent.

It is possible that including a plasticizer in the present effervescent granules will alter its rate of effervescence. Generally, increasing the amount of plasticizer present will increase or prolong the time of effervescence.

The rate of effervescence can also be controlled by varying the hydrophilicity or hydrophobicity of the hot-melt extrudable binder. Generally, the more hydrophobic the binder, the slower the rate of effervescence. The solubility and rate of dissolution of a hydrophobic binder are important factors to consider as the level of binder in the effervescent granule is increased. For example, one can prepare an

effervescent granule having a rapid rate of effervescence by a water soluble hot-melt extrudable binder such as an electrolyte or nonelectrolyte such as xylitol, which can form a eutectic mixture with an appropriate acidic agent during hot-melt extrusion.

Conversely, one can prepare an effervescent granule having a slow rate of effervescence by employing a poorly water soluble hot-melt extrudable binder such as hydrogenated castor oil, lipids, wax, cholesterol, fatty acids or mono-, di- or triglycerides. Additionally, an effervescent granule having an intermediate rate of effervescence can be prepared by employing a binder, or combination of binders, such as those just discussed and optionally a surface active agent or cosolvent that improves wetting or disintegration of the effervescent granule.

Thus, rate of effervescence of the effervescent granule can be controlled by: (1) varying the relative amounts of the components; (2) optionally forming a eutectic mixture between the acidic agent and hot-melt extrudable binder; (3) varying acidic agent: alkaline agent ratio; (4) hydrophilicity vs. hydrophobicity of hot-melt extrudable binder; (5) varying the effervescent couple: hot-melt extrudable binder ratio; and (6) varying the amount of plasticizer present.

It should also be noted that when the effervescent granules are included in a tablet form, the hardness of a tablet may also play a role in disintegration time. Specifically, increasing the hardness of a tablet can increase the disintegration time just as decreasing hardness may decrease disintegration time. The hardness of the tablet can be controlled by the pressure used on the punches to compress the effervescent granule-containing formulation and by the amount of effervescent granules, concentration of effervescent couple, and amounts of drug and other excipients present in the tablet composition.

The effervescent granules of the invention can be included in formulations containing active ingredients. As used herein, the term "active ingredient" means a therapeutic compound, a flavoring agent, a sweetening agent, a vitamin, cleansing agent and other such compounds for pharmaceutical, veterinary, horticultural, household, food, culinary, pesticidal, agricultural, cosmetic, herbicidal, industrial, cleansing, confectionery and flavoring applications. When the effervescent granules are formulated into tablets, such tablets can also contain coloring agents, non-effervescent disintegrants, lubricants and the like. The effervescent granules of the invention can be formulated in a variety of forms such as a tablet, capsule, suspension, reconstitutable powder and suppository.

When a formulation including the effervescent granules and a therapeutic compound is included in a pharmaceutical tablet, the tablet's size and shape can be adapted for direct oral administration to a patient, such as a human patient. The pharmaceutical tablet is substantially completely disintegrable upon exposure to water and/or saliva. The effervescent granule is present in an amount effective to aid in disintegration of the tablet, and to provide a distinct sensation of effervescence when the tablet is placed in the mouth of a patient.

The effervescent sensation is not only pleasant to the patient but also tends to stimulate saliva production, thereby providing additional water to aid in further effervescent action. The patient should be able to perceive a distinct sensation of "fizzing" or bubbling as the tablet disintegrates in the mouth. To provide this sensation, the amount of effervescent granule in each tablet desirably is arranged to provide about 20 to about 60 cm^3 of gas. The "fizzing" sensation substantially enhances the organoleptic effects of the tablet. Thus, the amount of effervescent granule useful in accordance with the present invention is also an amount effective to provide a positive organoleptic sensation to a patient. A "positive" organoleptic sensation is one which is pleasant or enjoyable and which can be perceived readily by a normal human being. Thus, once the tablet is placed in the patient's mouth, it will disintegrate substantially completely without any voluntary action by the patient. Even if the patient does not chew the tablet, disintegration will proceed. Upon disintegration of the tablet, the therapeutic compound, which itself can be particulate, is released and can be swallowed as a slurry or suspension.

The mass of each such pharmaceutical tablet generally should be less than about 2.0 g and preferably less than about 0.5 g. The tablet may include surface markings, cuttings, grooves, letters and or numerals for the purpose of decoration and/or identification. Preferably, the tablet is a compressed tablet. It includes effervescent granules, together with a therapeutic compound and other components. The size of the tablet is also dependent upon the amount of material used. Circular, disk-like tablets desirably have diameters of about 11/16 inch or less, whereas elongated tablets desirably have a long dimension of about 7/8 inch or less.

The amount of effervescent granules of the present invention useful for the formation of tablets, in general, according to the present invention should range from about 2 to about 90% by weight of the final tablet composition, and preferably between about 5 and about 40% by weight thereof. In a more preferred embodiment, the amount of effervescent granule according to the present invention ranges from between about 3 and about 8% by weight of the final tablet composition.

Non-effervescent disintegrants include starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pecitin and tragacanth. Disintegrants can comprise up to about 20 weight percent and preferably between about 2 and about 10 percent of the total weight of the composition.

Coloring agents can include titanium dioxide, and dyes suitable for food such as those known as F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, etc. The amount of coloring used can range from about 0.1 to about 3.5 weight percent of the total composition.

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors which have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors may be present in an amount ranging from about 0.5 to about 3.0 by weight based upon the weight of the composition. Particularly preferred flavors are the grape and cherry flavors and citrus flavors such as orange.

Tablets according to this aspect of the present invention can be manufactured by well-known tableting procedures. In common tableting processes, material which is to be tableted is deposited into a cavity, and one or more punch members are then advanced into the cavity and brought into intimate contact with the material to be pressed, whereupon compressive force is applied. The material is thus forced into conformity with the shape of the punches and the cavity. Various tableting methods are well known to those skilled in the art and not detailed herein.

Materials to be incorporated in the tablets, other than the therapeutic compound and the effervescent granule can, be pretreated to form granules that readily lend themselves to tableting. This process is known as granulation. As commonly defined, "granulation" is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates to yield a free-flowing composition having a consistency suitable for tableting. Such granulated compositions may have consistency similar to that of dry sand. Granulation may be accomplished by agitation in mixing equipment or by compaction, extrusion or globulation.

As noted in Chapter 6 of Pharmaceutical Dosage Forms, supra, lubricants normally are used in manufacture of effervescent tablets. Without the use of an effective lubricant, tableting by use of high speed equipment would be difficult. Effervescent granulations are inherently difficult to lubricate due to both the nature of the raw materials and the requirement that the tablets disintegrate rapidly.

Lubricant, as used herein, means a material which can reduce the friction arising at the interface of the tablet and the die wall during compression and ejection thereof. Lubricants may also serve to prevent sticking to the punch and, to a lesser extent, the die wall as well. The term "antiadherents" is sometimes used to refer specifically to substances which function during ejection. As used in the present disclosure, however, the term "lubricant" is used generically and includes "antiadherents". Tablet sticking during formation and/or ejection may pose serious production problems such as reduced efficiency, irregularly formed tablets, and non-uniform distribution of intended agents or ingredients to be delivered thereby. These problems are particularly severe with high speed tableting approaches and methods.

Lubricants may be intrinsic or extrinsic. A lubricant which is directly applied to the tableting tool surface in the form of a film, as by spraying onto the die cavity and/or punch surfaces, is known as an extrinsic lubricant. Although extrinsic lubricants can provide effective lubrication, their use requires complex application equipment and methods which add cost and reduce productivity.

Intrinsic lubricants are incorporated in the material to be tableted. Magnesium, calcium and zinc salts of stearic acid have long been regarded as the most efficient intrinsic lubricants in common use. Concentrations of two percent or less are usually effective.

Other traditional intrinsic lubricants include hydrogenated and partially hydrogenated vegetable oils, animal fats, polyethyleneglycol, polyoxyethylene monostearate, talc, light mineral oils, sodium benzoate, sodium lauryl sulphate, magnesium oxide and the like. See European Patent Application No. 0,275,834, the disclosure of which is incorporated by reference. See also Leal, et al., U.S. Pat. No. 3,042,531.

Lubricants, according to the present invention, can be used in an amount of up to 1.5 weight percent and preferably between about 0.25 and about 1.0 weight percent of the total composition.

Intrinsic lubricants pose certain serious difficulties when used in conventional tablets. Many lubricants materially retard the disintegration of non-effervescent tablets. However, the effervescent granules used in the dosage form of the present invention overcome any such retardation. In dissolution of conventional effervescent tablets, the lubricant may cause "scumming" and/or agglomeration. Stearates, for example leave an objectionable "scum" when an effervescent tablet is placed in a glass of water. This "scum" reduces the aesthetic appeal of the solution made from an effervescent dosage form. However, because the tablets of the present invention dissolve in the mouth, the solution is never seen by the user. Therefore, the propensity of a lubricant to "scum" is of less importance. Thus, lubricants which can cause dissolution or scumming problems in other dosage forms can be used in dosage forms according to the present invention without material adverse effect.

The therapeutic compound included in a dosage form including the effervescent granules according to the invention can include at least one psychotropic drug such as a sedative, antidepressant, neuroleptic, or hypnotic. The present invention is especially valuable with psychotropic drugs in that a patient receiving such drugs, particularly a patient in a mental institution, often attempts to hold a conventional pharmaceutical tablet or capsule concealed within his mouth rather than swallow it. The patient may then surreptitiously remove the tablet or capsule when medical personnel are not present. The preferred dosage forms according to this aspect of the present invention are substantially resistant to such concealment, inasmuch as they will disintegrate rapidly even if they are concealed within the mouth.

As the therapeutic compound, use can be of synthetic antibacterial agents of hardly water-soluble pyridonecarboxylic acid type such as benofloxacin, nalidixic acid, enoxacin, ofloxacin, amifloxacin, flumequine, tosfloxacin, piromidic acid, pipemidic acid, miloxacin, oxolinic acid, cinoxacin, norfloxacin, ciprofloxacin, pefloxacin, lomefloxacin, enrofloxacin, danofloxacin, binfloxacin, sarafloxacin, ibafloxacin, difloxacin and salts thereof. Other therapeutic compounds which can be formulated along with the effervescent granules into an effervescent solid dosage form include penicillin, tetracycline, erythromycin, cephalosporins and other antibiotics.

The therapeutic compounds which can be formulated in suitable dosage forms along with the effervescent granules of the invention also include antibacterial substances, antihistamines and decongestants, anti-inflammatories, antiparasitics, antivirals, local anesthetics, antifungal, amoebicidal, or trichomonocidal agents, analgesics, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives and muscle relaxants. Representative antibacterial substances are beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone. Representative antihistamines and decongestants are perilamine, chlorpheniramine, tetrahydrozoline and antazoline. Representative anti-inflammatory drugs are cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide. A representative antiparasitic compound is ivermectin. Representative antiviral compounds are acyclovir and interferon. Representative analgesic drugs are diflunisal, aspirin

or acetaminophen. Representative antiarthritics are phenylbutazone, indomethacin, silindac, its salts and corresponding sulfide, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone or probenecid. Representative antiasthma drugs are theophylline, ephedrine, beclomethasone dipropionate and epinephrine. Representative anticoagulants are heparin, bishydroxycoumarin, and warfarin. Representative anticonvulsants are diphenylhydantoin and diazepam. Representative antidepressants are amitriptyline, chlordiazepoxide perphenazine, protriptyline, imipramine and doxepin. Representative antidiabetics are insulin, somatostatin and its analogs, tolbutamide, tolazamide, acetchexamide and chlorpropamide. Representative antineoplastics are adriamycin, fluorouracil, methotrexate and asparaginase. Representative antipsychotics are prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline and trifluopromazine. Representative antihypertensives are spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine. Representative muscle relaxants are succinylcholine-chloride, danbrolene, cyclobenzaprine, methocarbamol and diazepam.

The therapeutic compound(s) contained within a formulation containing effervescent granules can be formulated as its pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent pharmacologically active compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent therapeutic compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a predetermined amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B12, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins. Coenzymes include thiamine pyrophosphates (TPP), flavin mononucleotide (FMM), flavin adenine dinucleotive (FAD), Nicotinamide adenine dinucleotide (AND), Nicotinamide adenine dinucleotide phosphate (NADP) Coenzyme A (CoA) pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B12, lipoyllysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, camitine, and alpha, beta, and gamma carotenes.

As used in this disclosure, the term "mineral" refers to inorganic substances, metals, and the like required in the human diet. Thus, the term "mineral" as used herein includes, without limitation, calcium, iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium and the like, and mixtures thereof.

The term "dietary supplement" as used herein means a substance which has an appreciable nutritional effect when administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, and fish oils, amino-acids, proteins and mixtures thereof As will be appreciated, dietary supplements may incorporate vitamins and minerals.

The amount of therapeutic compound incorporated in each tablet may be selected according to known principles of pharmacy. An effective amount of therapeutic compound is specifically contemplated. By the term effective amount, it is understood that, with respect to for example pharmaceuticals, a pharmaceutically effective amount is contemplated. A pharmaceutically effective amount is the amount or quantity of a drug or pharmaceutically active substance which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient. As used with reference to a vitamin or mineral, the term "effective amount" means an amount at least about 10% of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient. For example, if an intended ingredient is vitamin C, then an effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

The therapeutic compound is used in finely divided form, i.e. powder or granulate so as to increase the dissolution rate. It is preferable to use a finely powdered therapeutic compound to increase the dissolution rate, more preferably, the therapeutic compound being capable of allowing not less than 80%, desirably not less than 90% of it to pass through a 100 mesh (150 mu m) screen. The amount of therapeutic compound to be incorporated ranges usually from about 0.1 to 50%, preferably about 1 to 25% by weight based on the effervescent composition, and the ratio may be suitably modified depending on the therapeutic compound then employed. When the therapeutic compound is an acid substance capable of effervescing by reaction with carbonate, the therapeutic compound itself may be used as the acidic agent, and, in this case, an acidic agent for use as set forth below may be optionally added further.

When the effervescent granules of the invention are formulated into a reconstitutable powder for a carbonated beverage, they can be prepared according to Example 4 or other suitable method known to those of skill in the art.

The effervescent granules formulated into a suppository can be used to treat vaginal infection and adjust vaginal pH. Such a formulation can be prepared according to example 5, or other method well known to those of skill in the art.

Suspensions containing the effervescent granules of the invention and a herbicide can be used in agricultural applications. Such formulations can comprise a reconstitute powder according to example 6, which is suspended in a liquid prior to use.

Hot Melt Extrusion

In one aspect of this invention, the effervescent granule is produced by a hot-melt extrusion method as shown below. An acidic agent and an alkaline agent, preferably a carbon dioxide precursor, and a hot-melt extrudable binder, all in a dry state, are placed into a mixer or hopper and agitated (blended) until thoroughly mixed to form an effervescent mixture. The effervescent mixture is then hot-melt extruded at a rate and temperature sufficient to melt or soften the binder, to minimize degradation of the components and to form an extrudant which is subsequently ground or chopped into effervescent granules.

In another aspect of the invention, the effervescent granule is produced by a hot melt extrusion process as follows. An acidic agent and a hot-melt extrudable binder, capable of forming a eutectic mixture with the acidic agent, are placed into a mixer and agitated until thoroughly mixed to form a mixture which is hot-melt extruded and ground to form a granular eutectic mixture. An alkaline agent, such as a carbon dioxide precursor, is added to the granular eutectic mixture and thoroughly blended to form an effervescent mixture. The effervescent mixture is then hot-melt extruded at a rate and temperature sufficient to melt or soften the eutectic mixture, to minimize degradation of the components, e.g. degradation of $NaHCO_3$ to Na_2CO_3, and to form an extrudant which is subsequently ground or chopped into effervescent granules.

As used herein, the term "effervescent mixture" means a granular or particulate mixture comprising an acidic agent, an alkaline agent and a hot-melt extrudable binder which when placed in water will cause effervescence. As used herein, the term "eutectic mixture" means a mixture of an acidic agent and a hot-melt extrudable binder that has been hot-melt extruded and that melts or softens at a temperature lower than the melting or softening temperature of the hot-melt extrudable binder neat. The eutectic mixture can be a full or partial mixture and can be referred to as a "solid solution."

The rate at which the hot-melt extrusion is conducted can also vary widely. The rate will be such that degradation of the components of the mixture being extruded will be minimized. Such rate can be easily determined experimentally and will vary according to the particular mixture being extruded. Generally, the extrusion rate is such that the time of exposure of the components to the elevated temperature is less than 5 minutes and preferably less than 2 minutes.

The rate of effervescence can be controlled by varying the rate of hot-melt extrusion. Generally, increasing the rate of hot-melt extrusion of the effervescent granule will increase the rate of effervescence. This is especially true for hot-melt extrudable binders having melting or softening points greater than about 100 c. Conversely, decreasing the rate of hot-melt extrusion of effervescent granule will generally decrease the rate of effervescence.

The hot-melt extrusion process preferably employed is conducted at an elevated temperature, i.e. the heating zone (s) of the extruder is above room temperature (about 20° C.). It is important to select an operating temperature range that will minimize the degradation or decomposition of the effervescent composition during processing. The operating temperature range is generally in the range of from about 50° C. to about 150° C. as determined by the setting for the extruder heating zone(s). The temperature of the mixture being hot-melt extruded will not exceed 150° C. and preferably will not exceed 120° C. The hot-melt extrusion is conducted employing a dry granular or powdered feed.

The extruder used to practice the invention can be any such commercially available model equipped to handle dry feed and having a solid conveying zone, one or multiple heating zones, and an extrusion die. A two stage single screw extruder, such as that manufactured by BRABENDER or KILLION are two such apparati. It is particularly advantageous for the extruder to possess multiple separate temperature controllable heating zones.

Many conditions can be varied during the extrusion process to arrive at a particularly advantageous formulation. Such conditions include, by way of example, formulation composition, feed rate, operating temperature, extruder screw RPM, residence time, die configuration, heating zone length and extruder torque and/or pressure. Methods for the optimization of such conditions are known to the skilled artisan.

When higher melting temperature, higher molecular weight or high softening temperature binders are employed, the hot-melt extrusion may require higher processing temperature, pressure and/or torque than when binders having a lower molecular weight, melting or softening temperature are employed. By including a plasticizer, and, optionally, an antioxidant, in a formulation, processing temperature, pressure and/or torque may be reduced. Plasticizers are not required in order to practice the invention. Their addition to the formulation is contemplated as being within the scope of the invention. Plasticizers are advantageously included in the effervescent granules when hot-melt extrudable binders having a melting or softening point temperature greater than 150° C. are employed.

As used herein, the term "plasticizer" includes all compounds capable of plasticizing the hot-melt extrudable binder of the invention. The plasticizer should be able to lower the melting temperature or glass transition temperature (softening point temperature) of the hot-melt extrudable binder. Plasticizers, such as low molecular weight PEG, generally broaden the average molecular weight of the hot-melt extrudable binder thereby lowering its glass transition temperature or softening point. Plasticizers also generally reduce the viscosity of a polymer melt thereby allowing for lower processing temperature and extruder torque during hot-melt extrusion. It is possible the plasticizer will impart some particularly advantageous physical properties to the effervescent granules.

Plasticizers useful in the invention can include, by way of example and without limitation, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly (propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin.

Such plasticizers can also be ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutylsebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co.

It is contemplated and within the scope of the invention, that a combination of plasticizers may be used in the present formulation. One advantageous combination is that comprised of poly(ethylene glycol) and low molecular weight poly(ethylene oxide). The PEG based plasticizers are available commercially or may be made by a variety of methods, such as disclosed in *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J M Harris, Ed.; Plenum Press, N.Y.) the teachings of which are hereby incorporated by reference.

The amount of plasticizer used in the effervescent granules will depend upon its composition, physical properties, effect upon the effervescent granules, interaction with other components of the granules and other such reasons. Generally, the plasticizer content will not exceed about 40% wt. of the formulation.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

One embodiment of the present invention provides an effervescent granule having a controllable rate of effervescence comprising:

a hot-melt extrudable binder present in the amount of about 3% to about 8% by weight of said effervescent granule, said binder being capable of forming a eutectic mixture with an acidic agent;

an acidic agent; and

an alkaline agent; said effervescent granule being made by a process comprising:

dry blending and hot-melt extruding said acidic agent and said hot-melt extrudable binder to form an acidic mixture; and

dry blending and hot-melt extruding the acidic mixture and said alkaline agent to form said effervescent granule.

Another embodiment of the present invention provides a hot-melt extrusion process for preparing an effervescent granule having a controllable rate of effervescence, said process comprising:

dry blending and hot-melt extruding an acidic agent, a hot-melt extrudable binder and a plasticizer to form a eutectic mixture; and

dry blending and hot-melt extruding the eutectic mixture and an alkaline agent to form said effervescent granule.

The foregoing will be better understood with reference to the following examples which detail certain procedures for the manufacture of tablets according to the present invention. All references made to these examples are for the purposes of illustration. They are not to be considered limiting as to the scope and nature of the present invention.

EXAMPLE 1

PREPARATION OF EFFERVESCENT GRANULES

The following general procedure can be used to prepare a variety of effervescent granules according to the present invention.

All materials to be used are passed through a fine screen (100 mesh). The materials are then dried at 40° C. for 24 hours, preferably in a vacuum. The following steps are conducted in an atmosphere having a low relative humidity. All materials are then mixed in a twin shell blender for 5–10 minutes until a uniform blend is achieved. Then, using a hot-melt extrusion apparatus, the powder blend is subjected to a temperature of less than or equal to about 1 20° C. at a rate and for a period of time sufficient to melt or soften the binder to form agglomerates of the effervescent couple in an extrudant which is either chopped or ground. The extruded granules are then screened and stored at a low relative humidity for subsequent incorporation into a variety of pharmaceutical dosage forms.

The following materials can be used to prepare the effervescent granules according to the procedure just described.

A.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	52
	Citric Acid	14
	Tartaric Acid	28
	PEG 1,000	6

B.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	55
	Citric Acid	13.5
	Tartaric Acid	24
	PEG 4,000	7.5

C.	Ingredients	Amount (% Wt.)
	Sodium Glycine Carbonate	58
	Citric Acid	15
	Tartaric Acid	21
	Pluronic F68	6

D.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	54
	Citric Acid	16
	Tartaric Acid	24
	PEG 20,000	3
	PEG 400	3

E.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	50
	Citric Acid	14
	Tartaric Acid	28
	PEG 8,000	8

F.	Ingredients	Amount (% Wt.)
	$KHCO_3$	62
	Fumaric Acid	5
	Citric Acid	8
	Tartaric Acid	18
	PEG 6,000	7

G.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	55
	NaH_2PO_4	37.5
	Pluronic F127	7.5

H.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	54
	Fumaric Acid	3
	Maleic Acid	5
	Citric Acid	13
	Tartaric Acid	18
	PEG 3,350	6
	Pluronic F68	4

I.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	56
	Citric Acid	37
	Cetyl alcohol	4
	Stearyl alcohol	5

-continued

J.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	51
	Citric Acid	34
	Xylitol	15

K.	Ingredients	Amount (% Wt.)
	$NaHCO_3$	50
	Citric Acid	40
	Xylitol	10

In example K, xylitol and citric acid are first hot melt extruded to form a eutectic mixture which is then hot melt extruded with NaHCO3 to form the effervescent granule.

Table 1 is presented to demonstrate the utility of the present invention as used together with granules that effervesce relatively rapidly in the presence of water. These granules may then be formulated into a tablet or other dose compatible and convenient form. These granules are to be prepared by hot melt extrusion as described herein, as well as modified processes thereof.

TABLE 1

	Rapidly effervescent granules in contact with water. HME-EC Granulations			
Excipient	Formulation L % w/w	Formulation M % w/w	Formulation N % w/w	Formulation O % w/w
PEG 3350	10	10	10	10
Sodium Bicarbonate	10	10	10	10
Sodium Carbonate, fine powder	30	0	0	0
Potassium Carbonate, fine powder	0	25	28	30
Citric Acid, anhydrous	40	35	37	40
Xylitol, granular	0	0	8	10
Xylitol, fine powder	0	10	0	0
Kollodion ® CL	10	10	0	0
AcDiSol ®	0	0	7	0

Table 2 is presented to demonstrate the utility of the above described rapidly effervescence granules that contain xylitol. These granules are prepared by a hot-melt extrusion process.

TABLE 2

	HME-EC Granules With Xylitol			
Excipient	Formulation P % w/w	Formulation Q % w/w	Formulation R % w/w	Formulation S % w/w
PEG 3350	6.5	6.5	6.5	6.5
Sodium Bicarbonate	10	10	10	10
Sodium Carbonate, fine powder	30	0	0	0
Potassium Carbonate, fine powder	0	25	28	30
Citric Acid, anhydrous	40	35	37	40
Xylitol, granular		3.5	8	10
Xylitol, fine powder	3.5	10	3.5	3.5
Kollodion ® CL	10	10	0	0
AcDiSol ®	0	0	7	0

EXAMPLE 2

DETERMINATION OF EFFERVESCENT GRANULE DISSOLUTION RATE

This is a visual end-point test for determining effervescent granule solubility.

Effervescent granules (2.0 grams) were added rapidly in one portion to a very gently stirred (less than 60 rpm) beaker containing water (1.0L) at about 20°–25° C. The endpoint was visually determined by observing cessation of effervescence or complete dissolution of effervescent granules.

EXAMPLE 3

PREPARATION OF TABLETS CONTAINING EFFERVESCENT GRANULES

The following general procedure can be used to prepare a wide variety of tablet dosage forms containing the effervescent granules of the invention. It should be understood that the ingredients listed below are merely representative and can be replaced by many other equivalent compounds. Any of the effervescent granules detailed here as granules A through S may be employed where effervescent granule (EG) is indicated in the following tablet formulations.

A.	Ingredients	Amount (% Wt.)
	Effervescent Granule (EG)	40
	Dicalcium Phosphate	10
	Microcrystalline Cellulose (MCC)	5
	Calcium Stearate	2.5
	Silicon Dioxide	1.0
	APAP	41.5

B.	Ingredients	Amount (% Wt.)
	EG	50
	Pseudoephedrine HCl	20
	Mannitol	29
	Magnesium Stearate	0.5
	Silicon Dioxide	0.5

C.	Ingredients	Amount (% Wt.)
	EG	25
	MCC	15
	Diltiazem	10
	Lactose	47
	Magnesium Stearate	0.5
	Silicon Dioxide	0.5
	Aspartame	1.0
	Grape Flavor	1

D.	Ingredients	Amount (% Wt.)
	APAP	60
	EG (C)	8
	Mannitol	30
	Aspartame	1.5
	Magnesium Stearate	0.5

(C) refers to EG made according to Example 1 using ingredients listed under C.

E.	Ingredients	Amount (% Wt.)
	Aspirin	50
	Mannitol	15
	AVICEL PH101	25.5
	Aspartame	1.5
	Stearic Acid	2.0
	EG (B)	6.0

-continued

F.	Ingredients	Amount (% Wt.)
	APAP	55
	ACT-DI-SOL	3
	EG (A)	8
	AVICEL PH101	10
	Mannitol	22
	Aspartame	1.5
	Magnesium Stearate	0.5

G.	Ingredients	Amount (% Wt.)
	CPM	1
	EG (A)	8
	AVICEL PH101	26.5
	Mannitol	62
	Magnesium Stearate	0.5
	Aspartame	2.0

Table 3 is presented to demonstrate effevesing granules in a convenient dose form. In this table, the dose form is a tablet. However, any number of other dose forms may be employed in providing a patient ready therapeutic of the present granulations.

TABLE 3

Hot-Melt Extruded - Effervescent Couple
(Tablet Formulations)
Effervescent tablets contains effervescent granules prepared by hot-melt extrusion.

Tablet Formulation H % w/w	Excipient	Tablet Formulation I % w/w
32.0	APAP	32.0
20.0 (formulation y)	EG	25.0 (granulation s)
28.0	Mannitol, fine powder	26.0
8.0	Emcocel ® LM50	5.0
5.0	Kollodion ® CL	5.0
5.0	Aspartame	5.0
0.7	Flavor, grape	0.7
0.4	Lake, lavender	0.4
0.3	Cab-O-Sil ® M5P	0.3
0.6	Magnesium Stearate	0.6

Generally, the listed ingredients are thoroughly mixed in a low relative humidity environment to form a tableting mixture. All the ingredients will generally pass through a 20 mesh screen. The tableting mixture is tableted in a conventional tableting press.

EXAMPLE 4

PREPARATION OF EFFERVESCENT RECONSTITUTABLE DRY BEVERAGE BASE

The following ingredients are thoroughly mixed in the amounts specified: Fries & Fries grapefruit flavoring #91470 (5.0 g), fructose USP (30.0 g), aspartame (0.5 g), and effervescent granule (2.0 g, prepared according to Example 1B). An active ingredient can optionally be added to this formulation. The above mixture will generally be reconstituted by adding water until solids reach 10 % by weight of the final formulation.

EXAMPLE 5

DRUG-CONTAINING HOT MELT EXTRUDABLE EFFERVESCENT GRANULATIONS

The following examples are presented to demonstrate the utility of the present invention in the preparation of drug-

containing granules. The drugs identified in Table 4 are for representative purposes only, as many other pharmacologically agents may be simularly included alone or in combination in the granulation process employing techniques known to those of ordinary skill in the art.

TABLE 4

Drug-Containing Hot-Melt Extruded Effervescent Formulations

Ibuprofen	50	50	0	0	0	30
Chlorphesinamine Maleate	0	0	5	5	0	5
Pseudoephridine HCl	0	0	0	25	20	
AcDiSol	5	5	0	0	5	5
Microcrystalline Cellulose	20	10	32	20		5
Na Bicarbonate	13	13	15	18	20	15
Citric Acid	12	12	14	15	18	13
PEG 3350	0	10	14	12	10	12
Crosslinked PVP	0	0	5	3	3	3
Explotab	0	0	0	2		2
Mannitol	0	0	5		9	
Xylitol	0	0	10		15	10

EXAMPLE 6

PREPARATION OF EFFERVESCENT SUSPENSION

The following ingredients are thoroughly mixed in the amounts specified: effervescent granule (59 g), bentonite (35 g) and BENLATE (6 g, from E. I. DuPont). The resulting mixture is suspended by adding approximately 1000 mL of water prior to spraying.

It is contemplated that this preparation may be used for example as a spray suitable for application to plants. The instantaneous dispersion of active ingredients provided through use of the present formulations reduces caking and agglomeration of the active ingredient onto surfaces.

EXAMPLE 7

TABLETS

The present example is presented to demonstrate the formulation of tablets from the granules described herein.

The granules provided herein may be compressed into tablets with the optional addition of lubricants, glidants, disintegrants and other tablet excipients that are well known in the art.

After suitable processing of the granules to the desired particle size, the lubricants (e.g., 1%–1.5% @ stearic acid, magnesium stearate @ 0.05, Prv=Sodium stearyl fumarate @ 2%), glidants (talc, silicon dioxide, cabosil M5P) and/or other excipients (flavorants, disintegrants, colorants and anti-oxidants) that are known in the art, are blended prior to compression into tablets or other solid dosage forms known to those of skill in the art. These granulations may also be packaged for individual dosage use upon mixture with an appropriate liquid, such as water or other liquid vehicle suitable for ingestion.

The granules and tablets containing the granules of the invention may also include, by way of example, H2 antagonists (e.g., anitidine), cardio vascular drugs, (e.g., diltizan hydrochloride), local anesthetic (e.g., lidocaine hydrochloride), anti fungal agent (e.g., miconazole), antibiotics (e.g., erythromycin), ani-cancer agents (coated for gastric release) (e.g., methotrexate), and tranquilizers (e.g. amitryptoline).

EXAMPLE 8

PREPARATION OF A VAGINAL TABLET COMPRISING SLOWLY EFFERVESCING EFFERVESCENT GRANULES

One thousand layered tablets are prepared as follows:

(a) Miconazole: 300 gm
(b) Hydroxypropylmethylcellulose (400 cps): 100.0 gm
(c) Mannitol: 100.0 gm
(d) Corn starch: 6.0 gm
(e) Zinc stearate: 3.6 gm
(f) Effervescent granule (1E): 50 gm

Using a suitable mixer, the miconazole, mannitol and Hydroxypropylmethylcellulose are mixed well via geometric dilution. The mixture is mixed in a Fitzmill quipped with a No. 000 screen and granulated using a 5% starch paste prepared by adding the corn starch to approximately 115 ml of water. Additional water is added as required to make a suitable granulation. The resulting granulation is wet-screened using a No. 2 screen and tray dried at 40° C. to 50° C. for 8 to 12 hours. The dried granulation is ground and passed through a No. 10 screen. Zinc stearate and effervescent granule, which has passed through a No. 20 screen, is added to the granulation, mixed well and the resulting slow release effervescent granulation reserved for tablet compression.

Using a suitable layer press, such as the Manesty Layer Press, the slow release granulation is added to the adjusted die cavity to provide a layer having a weight of approximately 500 mg. The final compression pressure is adjusted to provide a suitable tablet with a total weight of approximately 0.5 g.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular embodiments disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by others without departing from the spirit and scope of the invention.

What is claimed is:

1. An effervescent granule comprising:

a mixture consisting essentially of an acidic agent, a pharmacologically active agent, a hot-melt extrudable binder and an alkaline agent;

the effervescent granule being made by an essentially water free and essentially solvent free thermal heat process comprising:

dry blending said mixture; and

hot-melt extruding said blended mixture to form an effervescent granule.

2. A thermal heat process for preparing an effervescent granule comprising:

an acidic agent;

an alkaline agent; and

a hot-melt extrudable binder,

the thermal heat process comprising:

dry blending said acidic agent, said alkaline agent and said hot-melt extrudable binder to form a first mixture; and

hot-melt extruding said mixture to form an effervescent granule.

3. An effervescent granule comprising:

a hot-melt extrudable binder present in the amount of about 3% to about 8% by weight of said effervescent granule, said binder being capable of forming a mixture with an acidic agent; and

an alkaline agent,

said effervescent granule being made by an essentially water free and solvent free thermal heat process comprising:

dry blending said acidic agent, alkaline agent and said hot-melt extrudable binder to form a mixture; and

hot-melt extruding the mixture to form said effervescent granule.

4. The thermal heat process for preparing an effervescent granule of claim **2** wherein the effervescent granule is further defined as comprising a non-steroidal anti-inflammatory agent.

5. The thermal heat process for preparing an effervescent granule of claim **2** wherein the effervescent granule further comprises ibuprofen, indomethacin, or a combination thereof.

6. The thermal heat process for preparing an effervescent granule of claim **2** wherein the effervescent granule further comprises an antihistamine.

7. The thermal heat process for preparing an effervescent granule of claim **2** wherein the effervescent granule further comprises chlorpheniramine maleate.

8. The thermal heat process for preparing an effervescent granule of claim **2** wherein the effervescent granule further comprises a non-steroidal anti-inflammatory agent and an antihistamine.

9. The thermal heat process for preparing an effervescent granule of claim **2** wherein said granule is formulated into a tablet.

10. The thermal heat process for preparing an effervescent granule of claim **2** further comprising a plasticizer.

11. The thermal heat process for preparing an effervescent granule of claim **2** where the effervescent granule further comprises a plasticizer.

12. An effervescent granule prepared by the thermal heat process of claim **2** wherein said granule comprises an antihistamine.

13. An effervescent granule prepared by the thermal heat process of claim **2** wherein said granule comprises chlorpheniramine maleate.

14. An effervescent granule prepared by the thermal heat process of claim **2**, wherein said granule comprises a non-steroidal anti-inflammatory agent and an antihistamine.

15. The effervescent granule of claim **12**, **13**, or **14** wherein said granule is formulated into a tablet.

16. The effervescent granule of claim **12**, **13**, or **14** wherein said granule comprises a plasticizer.

* * * * *

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

NOTICE OF ASSIGNMENT TO UNITED STATES MAGISTRATE JUDGE FOR DISCOVERY

This case has been assigned to District Judge David O. Carter and the assigned discovery Magistrate Judge is Robert N. Block.

The case number on all documents filed with the Court should read as follows:

SACV09- 1423 DOC (RNBx)

Pursuant to General Order 05-07 of the United States District Court for the Central District of California, the Magistrate Judge has been designated to hear discovery related motions.

All discovery related motions should be noticed on the calendar of the Magistrate Judge

==========

NOTICE TO COUNSEL

A copy of this notice must be served with the summons and complaint on all defendants (if a removal action is filed, a copy of this notice must be served on all plaintiffs).

Subsequent documents must be filed at the following location:

[ ] **Western Division**
312 N. Spring St., Rm. G-8
Los Angeles, CA 90012

[X] **Southern Division**
411 West Fourth St., Rm. 1-053
Santa Ana, CA 92701-4516

[ ] **Eastern Division**
3470 Twelfth St., Rm. 134
Riverside, CA 92501

Failure to file at the proper location will result in your documents being returned to you.

Name & Address:
Daniel M. Cislo
Cislo & Thomas LLP
1333 2nd Street, Suite 500
Santa Monica, CA 90401-4110

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

Alacer Corp., a California Corporation PLAINTIFF(S) v. Fortress Systems LLC, a Nebraska Limited Liability Corp. dba FSI Nutrition DEFENDANT(S).	CASE NUMBER SACV09-01423 DOC (RNBx) **SUMMONS**

TO: DEFENDANT(S): Fortress Systems LLC dba FSI Nutrition

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it), you must serve on the plaintiff an answer to the attached ☑ complaint ☐ _____ amended complaint ☐ counterclaim ☐ cross-claim or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff's attorney, Daniel M. Cislo, whose address is 1333 2nd Street, Suite 500, Santa Monica, CA 90401-4110. If you fail to do so, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

Clerk, U.S. District Court

Dated: - 4 DEC 2009

By: SHEA BOURGEOIS
Deputy Clerk

SEAL
(Seal of the Court)

[Use 60 days if the defendant is the United States or a United States agency, or is an officer or employee of the United States. Allowed 60 days by Rule 12(a)(3)].

CONFORM COPY

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

I (a) PLAINTIFFS (Check box if you are representing yourself ☐)	DEFENDANTS
Alacer Corp.	Fortress Systems LLC dba FSI Nutrition
(b) Attorneys (Firm Name, Address and Telephone Number. If you are representing yourself, provide same.)	**Attorneys (If Known)**
Cislo & Thomas LLP 1333 2nd Street, Suite 500 Santa Monica, CA 90401-4110	

II. BASIS OF JURISDICTION (Place an X in one box only.)

☐ 1 U.S. Government Plaintiff ☑ 3 Federal Question (U.S. Government Not a Party)

☐ 2 U.S. Government Defendant ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES - For Diversity Cases Only (Place an X in one box for plaintiff and one for defendant.)

	PTF	DEF		PTF	DEF
Citizen of This State	☑ 1	☐ 1	Incorporated or Principal Place of Business in this State	☑ 4	☐ 4
Citizen of Another State	☐ 2	☑ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☑ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN (Place an X in one box only.)

☑ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify): ☐ 6 Multi-District Litigation ☐ 7 Appeal to District Judge from Magistrate Judge

V. REQUESTED IN COMPLAINT: JURY DEMAND: ☑ Yes ☐ No (Check 'Yes' only if demanded in complaint.)

CLASS ACTION under F.R.C.P. 23: ☐ Yes ☑ No ☐ MONEY DEMANDED IN COMPLAINT: $ _____

VI. CAUSE OF ACTION (Cite the U.S. Civil Statute under which you are filing and write a brief statement of cause. Do not cite jurisdictional statutes unless diversity.)

Declatory Judgment of invalidity, non-infringement under 28 USC §§2201 and 2202 and Title 35 of the U.S. Code

VII. NATURE OF SUIT (Place an X in one box only.)

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Act
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Info. Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loan (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Fed. Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury-Méd Malpractice
- ☐ 365 Personal Injury-Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus-Alien Detainee
- ☐ 465 Other Immigration Actions

TORTS PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/Accommodations
- ☐ 444 Welfare
- ☐ 445 American with Disabilities - Employment
- ☐ 446 American with Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence Habeas Corpus
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus/ Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE / PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety /Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☑ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS-Third Party 26 USC 7609

FOR OFFICE USE ONLY: Case Number: _____

AFTER COMPLETING THE FRONT SIDE OF FORM CV-71, COMPLETE THE INFORMATION REQUESTED BELOW.

SACV09-01422

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

VIII(a). IDENTICAL CASES: Has this action been previously filed in this court and dismissed, remanded or closed? ☑ No ☐ Yes
If yes, list case number(s): _____

VIII(b). RELATED CASES: Have any cases been previously filed in this court that are related to the present case? ☑ No ☐ Yes
If yes, list case number(s): _____

Civil cases are deemed related if a previously filed case and the present case:
(Check all boxes that apply) ☐ A. Arise from the same or closely related transactions, happenings, or events; or
☐ B. Call for determination of the same or substantially related or similar questions of law and fact; or
☐ C. For other reasons would entail substantial duplication of labor if heard by different judges; or
☐ D. Involve the same patent, trademark or copyright, and one of the factors identified above in a, b or c also is present.

IX. VENUE: (When completing the following information, use an additional sheet if necessary.)

(a) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named plaintiff resides.
☐ Check here if the government, its agencies or employees is a named plaintiff. If this box is checked, go to item (b).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Orange	

(b) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named defendant resides.
☐ Check here if the government, its agencies or employees is a named defendant. If this box is checked, go to item (c).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
	Douglas

(c) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** claim arose.
Note: In land condemnation cases, use the location of the tract of land involved.

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country

*** Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, or San Luis Obispo Counties**
Note: In land condemnation cases, use the location of the tract of land involved

X. SIGNATURE OF ATTORNEY (OR PRO PER): _____ **Date** 12-4-09

Notice to Counsel/Parties: The CV-71 (JS-44) Civil Cover Sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law. This form, approved by the Judicial Conference of the United States in September 1974, is required pursuant to Local Rule 3-1 is not filed but is used by the Clerk of the Court for the purpose of statistics, venue and initiating the civil docket sheet. (For more detailed instructions, see separate instructions sheet.)

Key to Statistical codes relating to Social Security Cases:

Nature of Suit Code	Abbreviation	Substantive Statement of Cause of Action
861	HIA	All claims for health insurance benefits (Medicare) under Title 18, Part A, of the Social Security Act, as amended. Also, include claims by hospitals, skilled nursing facilities, etc., for certification as providers of services under the program. (42 U.S.C. 1935FF(b))
862	BL	All claims for "Black Lung" benefits under Title 4, Part B, of the Federal Coal Mine Health and Safety Act of 1969. (30 U.S.C. 923)
863	DIWC	All claims filed by insured workers for disability insurance benefits under Title 2 of the Social Security Act, as amended; plus all claims filed for child's insurance benefits based on disability. (42 U.S.C. 405(g))
863	DIWW	All claims filed for widows or widowers insurance benefits based on disability under Title 2 of the Social Security Act, as amended. (42 U.S.C. 405(g))
864	SSID	All claims for supplemental security income payments based upon disability filed under Title 16 of the Social Security Act, as amended.
865	RSI	All claims for retirement (old age) and survivors benefits under Title 2 of the Social Security Act, as amended. (42 U.S.C. (g))